PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No. : 10/680,881
Applicant : Hector F. DeLuca et al

Filed : October 8, 2003
Title : Treatment of Inflammatory Bowel Disease with 2-Methylene-19-Nor-Vitamin D Compounds

TC/A.U. : 1617
Examiner : Soroush, Layla

Docket No. : 1256-00918
Conf. No. : 6439

CERTIFICATE OF ELECTRONIC SUBMISSION

I hereby certify that this correspondence is being submitted electronically with the United States Patent and Trademark Office's electronic filing system (EFS Web) on this 23rd day of September, 2008.

9-23-08
Marie Mikolainis Date

DECLARATION OF HECTOR F. DELUCA

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Hector F. DeLuca, hereby declare as follows:

1. That I am one of the named inventors in the above-identified patent application;

2. That I am a Professor of Biochemistry in the College of Agricultural and Life Sciences at the University of Wisconsin-Madison, located in Madison, Wisconsin, and have been active in conducting research in the vitamin D field for more than 35 years;

3. That I have read and I am familiar with the Patent Office Action dated June 23, 2008 and the references cited therein and applied against the claims of the present application, namely, DeLuca et al U.S. Patent 6,392,071 and Wu U.S. Patent 5,981,597;

4. That based upon my experience in the vitamin D art and, particularly, because of my knowledge of the compounds of the present invention and those of the applied art, in which art (the '071 patent) I am named as a co-inventor and of which, therefore, I have intimate knowledge, and the unexpected activity which the present compounds exhibit, I disagree with the Examiner

that use of the compounds of the present invention for the treatment of ulcerative colitis would be obvious from the references applied, and that my position is fully supported by the following facts set forth herein;

5. That I had conducted and I supervised a series of tests in order to determine, evaluate and compare the activity of the following compounds in a mouse model of inflammatory bowel disease:

a) 1α,25-dihydroxyvitamin D_3 (referred to as 1,25D_3). See Exhibit A.

b) 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (E-isomer) (referred to as DPO29 or 1AGR). See Exhibit B.

c) 2-methylene-18,19-dinor-(20S)-1α,25-dihydroxyvitamin D_3 (referred to as DPO35 or VD-03). See Exhibit C.

d) 2-methylene-1α,25-dihydroxy-(17E)-17(20)-dehydro-19-norvitamin D_3 (referred to as DPO66 or Vit-III 17-20E). See Exhibit D.

6. That the first compound listed above is the compound specifically disclosed in Wu '597, and is not covered by the claims of the present patent application because the present claims require a methylene group attached at the carbon 2 position of the A-ring of the vitamin D nucleus, and 1,25D_3 does not contain a 2-methylene group. However, 1,25D_3 does have significant cell differentiation activity as reported in Wu and other references;

7. That the second compound listed above, namely DPO29 or 1AGR, is also not covered by the claims of the present patent application because it contains a hydroxy substituted alkylidene group attached at carbon 2 of the A-ring, whereas the present claims require only a methylene group attached to the carbon 2 position of the A-ring. However, DPO29 or 1AGR does, in fact, have significant cell differentiation activity as demonstrated by the data contained in U.S. Patent 7,241,747, attached hereto as Exhibit G;

8. That the third compound listed above, namely DPO35 or VD-03, is also not encompassed by the claims of the present patent application because although it contains a methylene group attached at the carbon 2 position of the A-ring, it is missing the methyl group at the carbon 18 position and is therefore an 18,19-dinor vitamin D compound, whereas the structure

set forth in claim 1 requires a methyl group attached at the carbon 18 position. However, the compound DPO35 has significant cell differentiation activity, as taught in U.S. Published Patent Application No. 2005/0227950A1, attached hereto as Exhibit H;

9. That the fourth compound listed above, namely DPO66 or Vit-III 17-20E, is also not covered by the claims of the present patent application because although it contains a methylene group attached at the carbon 2 position of the A-ring, and a methyl group at the 18 carbon position, it has a double bond extending between the 17 and 20 carbon positions, and is therefore referred to as a 17(20)-dehydro vitamin D compound, whereas the structure of claim 1 herein merely calls for a single bond extending between positions 17 and 20 of the vitamin D compound; however, the compound DP066 has significant cell differentiation activity, as taught in U.S. Patent 7,241,752B2, attaches as Exhibit I;

10. That the activity of all of these compounds were tested in a mouse model of inflammatory bowel disease wherein IL10 knockout mice were treated with piroxicam to accelerate and synchronize the disease;

11. That after the disease was established, the compounds were given to mice (N = 13 mice per treatment group) mixed in an agar diet for approximately four weeks;

12. That efficacy against inflammatory bowel disease was measured separately by two parameters, namely, (1) large intestinal weight and (2) distal pathological score (as assessed by an independent pathologist who was blinded to the treatment group assignments);

13. That the results of the tests are represented by the data set forth in Exhibits E and F, respectively, which are attached hereto;

14. That the data in Exhibits E and F show, as expected, $1,25D_3$ treatment resulted in decreased inflammatory bowel disease relative to the no treatment control group as assessed by large intestine weight (Exhibit E) as well as distal pathological score (Exhibit F);

15. That the compound 1AGR also resulted in a dose dependent decrease in the disease as assessed by large intestine weight (Exhibit E) as well as distal pathological score (Exhibit F);

16. That the two other compounds tested, namely DP035 and DP066, did not reduce inflammatory bowel disease significantly as determined by either large intestine weight (Exhibit

E) or distal pathological score (Exhibit F). Furthermore, at the higher dose, namely 1.8 μ/kg, DP066 did show a statistically significant increase in serum calcium, indicating that the drug was being delivered to the mice;

17. That, based upon the description in the Wu '597 reference, a person skilled in the vitamin D art would have expected, because Wu '597 indicated that vitamin D compounds have cell differentiation, that the compounds tested would all exhibit potent biological activity against inflammatory bowel diseases;

18. That, although all four compounds tested herein are vitamin D compounds, and all have significant cell differentiation activity, only $1,25D_3$ and 1AGR resulted in decreased inflammatory bowel disease, and the other two compounds tested, namely DPO35 and DPO66, did not reduce inflammatory bowel disease significantly by either assessment, despite the fact that they both have significant cell differentiation activity;

19. That, unexpectedly therefore, the compounds claimed in the present invention exhibit high biological activity against inflammatory bowel disease;

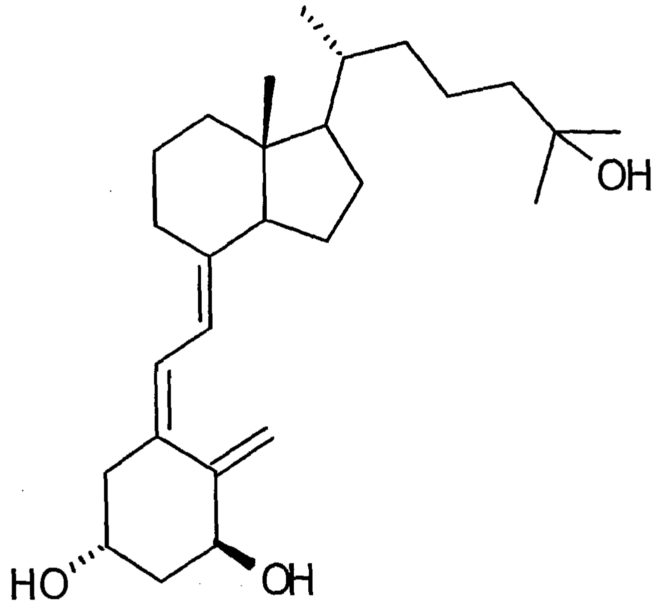
20. That the compounds of the present invention thus exhibit unexpected and unobvious biological properties.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

9/23/08
Date

Hector F. DeLuca

1α,25-dihydroxy-vitamin D3

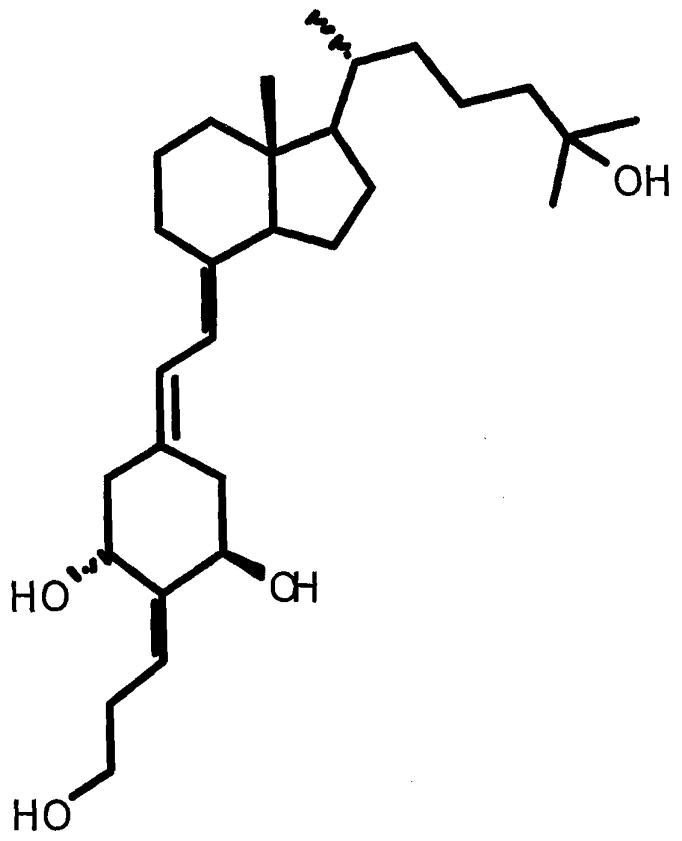


Molecular Weight = 416.65

Exhibit A

DP029 (or 1AGR)

2-(3'-hydroxypropylidene)-19-nor-1a,25-(OH)2D3 (E-isomer)

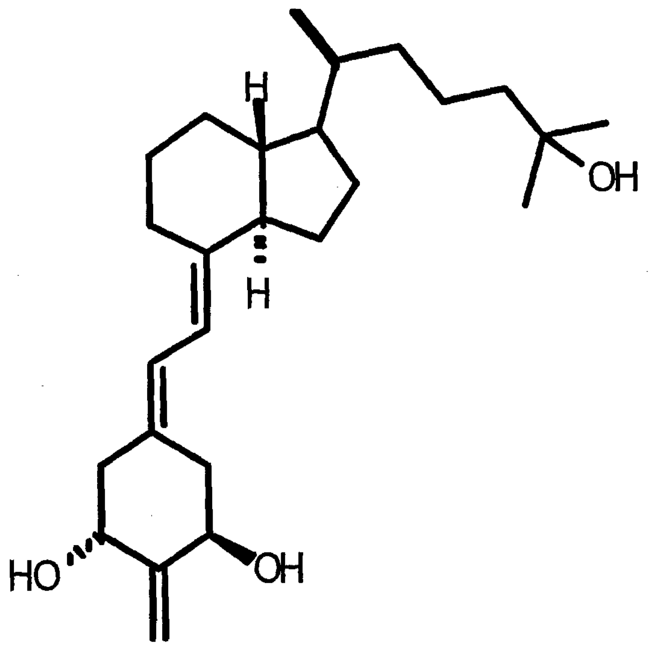


Molecular Weight = 460.70

Exhibit B

DP035 (VD-03)

2-methylene-18,19-dinor-(20S)-1a,25-dihydroxyvitamin D3

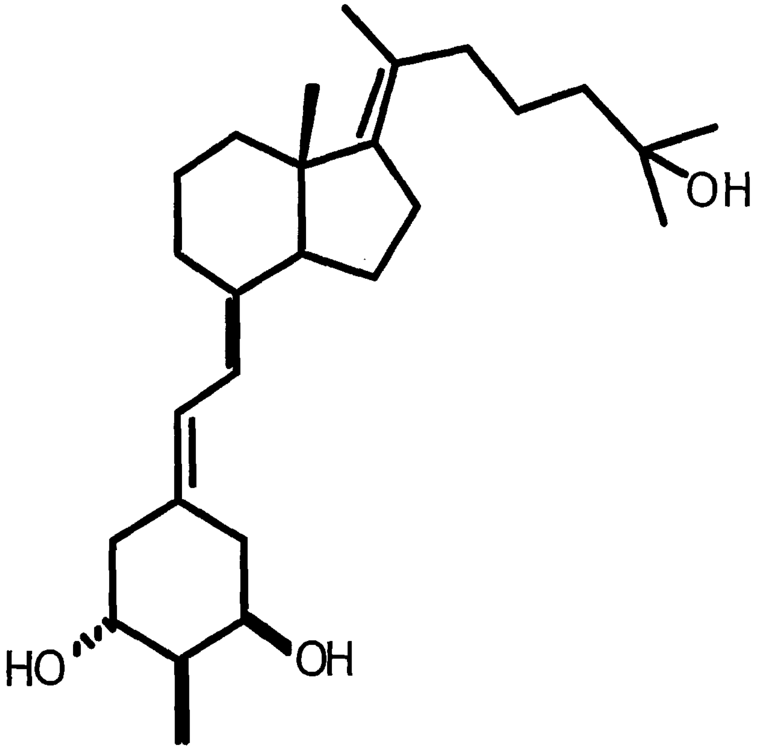


Molecular Weight = 402.62

Exhibit C

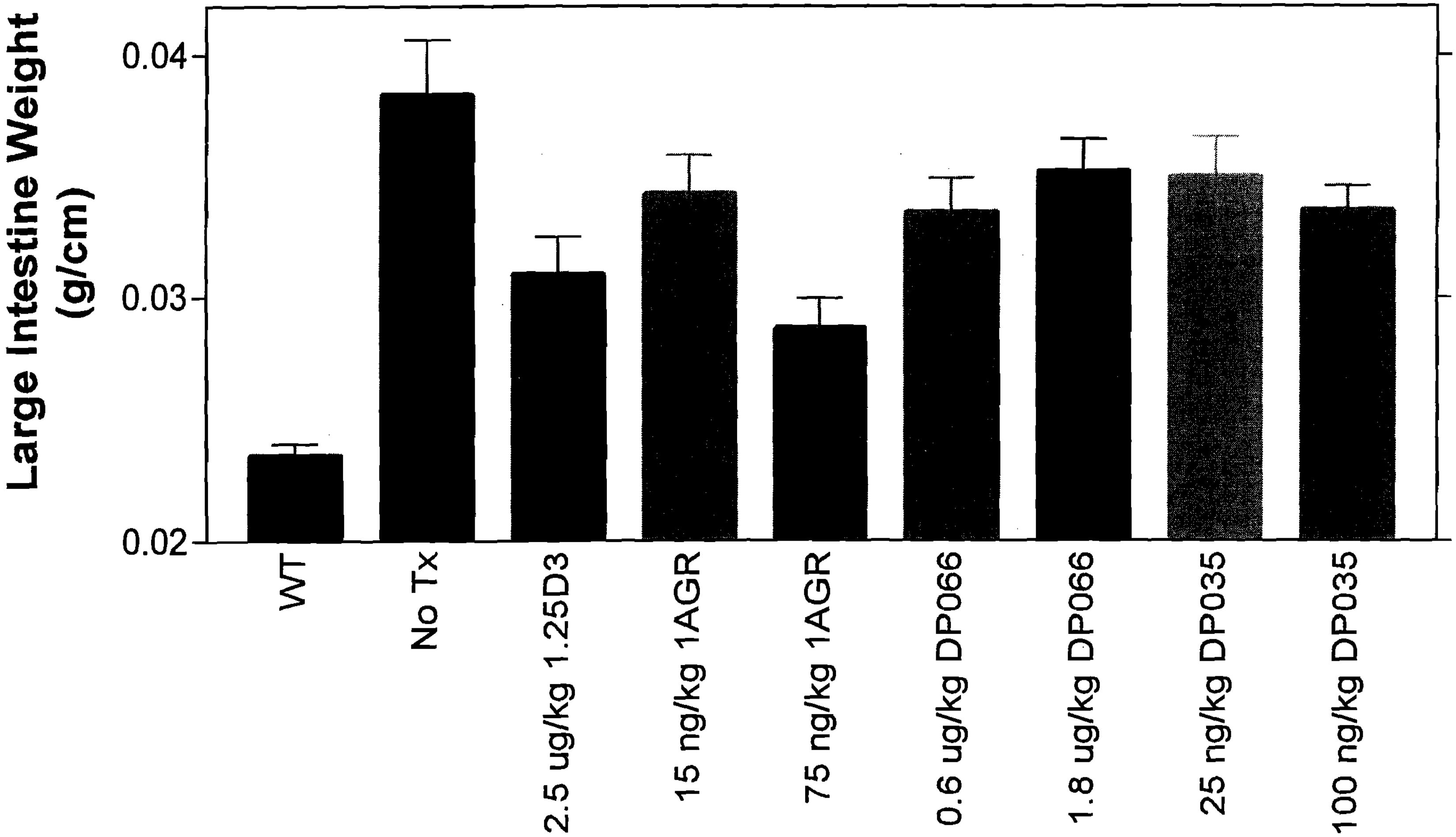
DP066 (or Vit-III 17-20E)

2-methylene-1a,25-dihydroxy-(17E)-17(20)-dehydro-19-norvitamin D3



Molecular Weight = 414.63

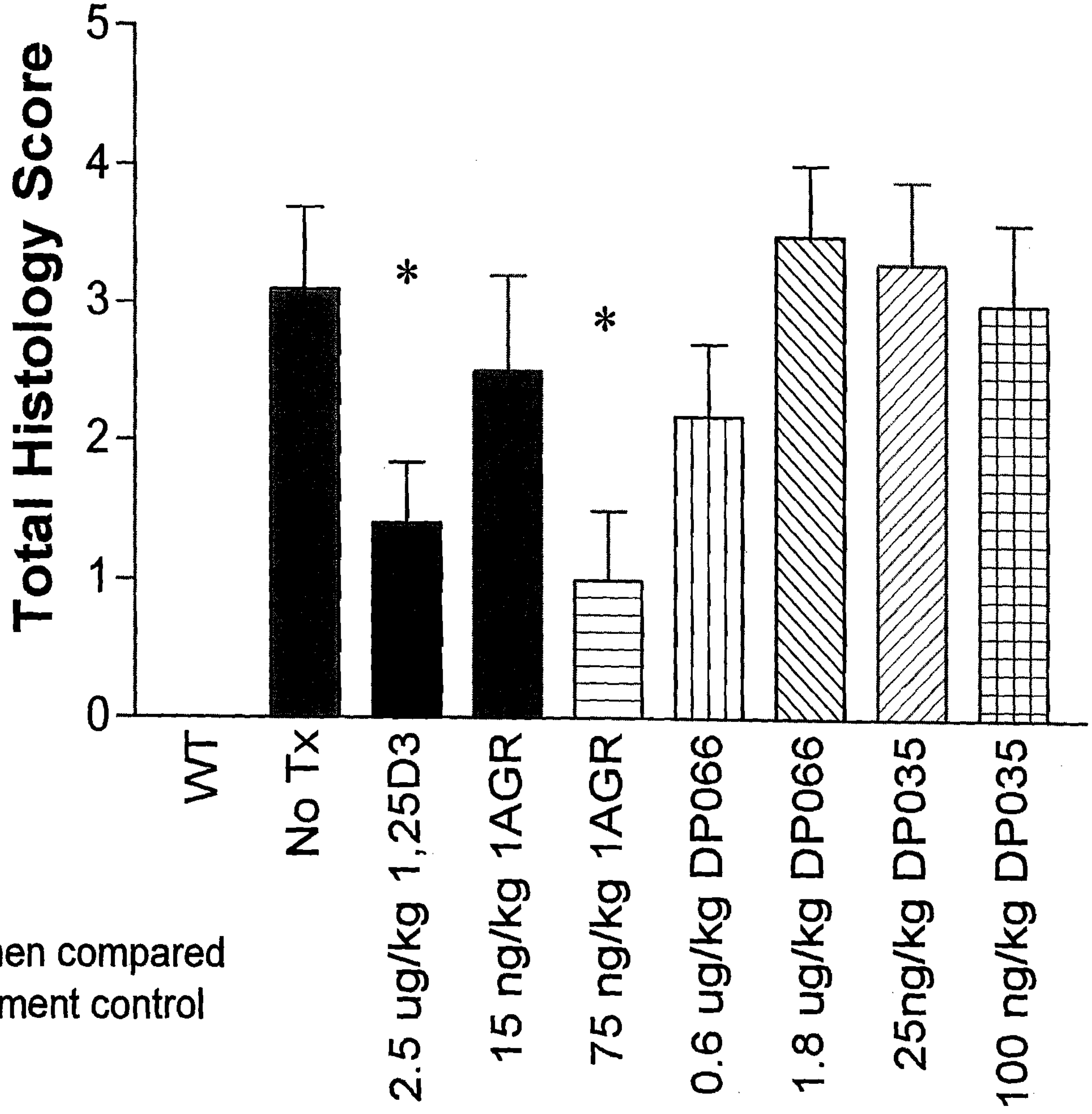
Exhibit D



Final Serum Ca	8.9 ±0.1	9.8 ±0.1	12.4 ±0.2	9.5 ±0.2	13.5 ±0.2	9.1 ±0.2	9.7 ±0.3	9.2 ±0.3	10.6 ± 0.2

Exhibit E

Exp. 14/16/17
Total Histology Score



P<0.05 when compared
to no treatment control
group

Exhibit F

Exhibit G

US007241747B2

(12) **United States Patent**
DeLuca et al.

(10) **Patent No.: US 7,241,747 B2**
(45) **Date of Patent: Jul. 10, 2007**

(54) 2-PROPYLIDENE-19-NOR-VITAMIN D COMPOUNDS

(75) Inventors: **Hector F. DeLuca**, Deerfield, WI (US); **Rafal R. Sicinski**, Warsaw (PL); **Agnieszka Glebocka**, Warsaw (PL); **Lori A. Plum**, Madison, WI (US)

(73) Assignee: **Wisconsin Alumni Research Foundation**, Madison, WI (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/821,479**

(22) Filed: **Apr. 9, 2004**

(65) **Prior Publication Data**

US 2004/0229851 A1 Nov. 18, 2004

Related U.S. Application Data

(60) Provisional application No. 60/461,958, filed on Apr. 10, 2003.

(51) **Int. Cl.**
A61K 31/59 (2006.01)
C07C 491/00 (2006.01)

(52) **U.S. Cl.** **514/167**; 552/653

(58) **Field of Classification Search** 552/653; 514/167

See application file for complete search history.

(56) **References Cited**

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(Continued)

Primary Examiner—Sabiha N. Qazi
(74) *Attorney, Agent, or Firm*—Andrus, Sceales, Starke & Sawall, LLP

(57) ABSTRACT

2-propylidene-19-nor-vitamin D compounds are disclosed as well as pharmaceutical uses for these compounds and methods of synthesizing these compounds. These compounds are characterized by high bone calcium mobilization activity and high intestinal calcium transport activity. This results in novel therapeutic agents for the treatment and prophylaxis of diseases where bone formation is desired, particularly osteoporosis, as well as autoimmune diseases such as multiple sclerosis, diabetes mellitus and lupus. These compounds also exhibit pronounced activity in arresting the proliferation of undifferentiated cells and inducing their differentiation to the monocyte thus evidencing use as an anti-cancer agent and for the treatment of skin diseases such as psoriasis. These compounds also increase both breaking strength and crushing strength of bones evidencing use in conjunction with bone replacement surgery such as hip and knee replacements.

103 Claims, 6 Drawing Sheets

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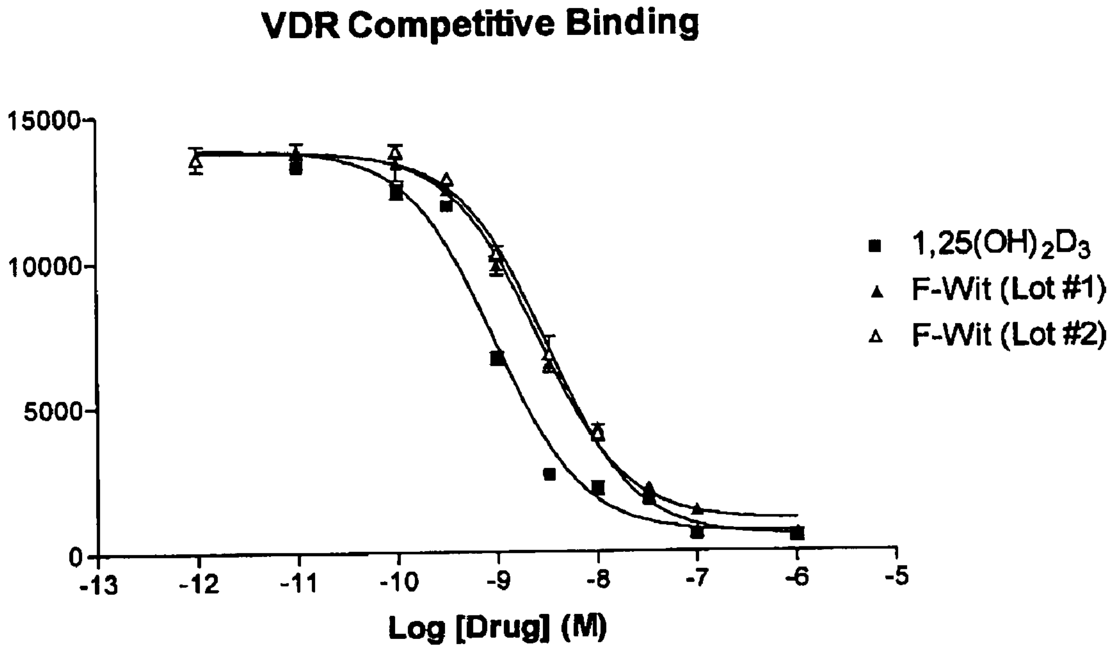

VDR Competitive Binding
15000
10000
5000
0
-13
-12
-11
-10
-9
-8
-7
-6
-5
Log [Drug] (M)
■ 1,25(OH)2D3
▲ F-Wit (Lot #1)
△ F-Wit (Lot #2)

Figure 1

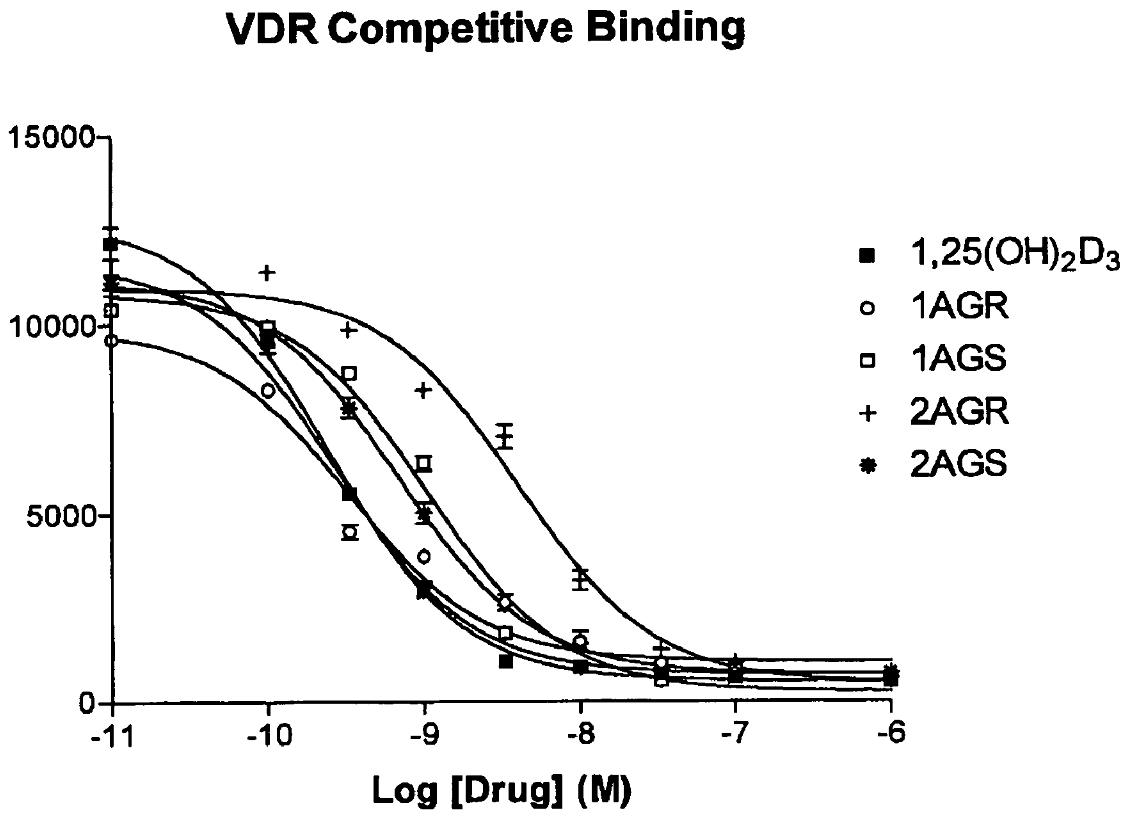

VDR Competitive Binding
15000
10000
5000
0
-11
-10
-9
-8
-7
-6
Log [Drug] (M)
■ $1,25(OH)_2D_3$
○ 1AGR
□ 1AGS
+ 2AGR
✱ 2AGS

Figure 2

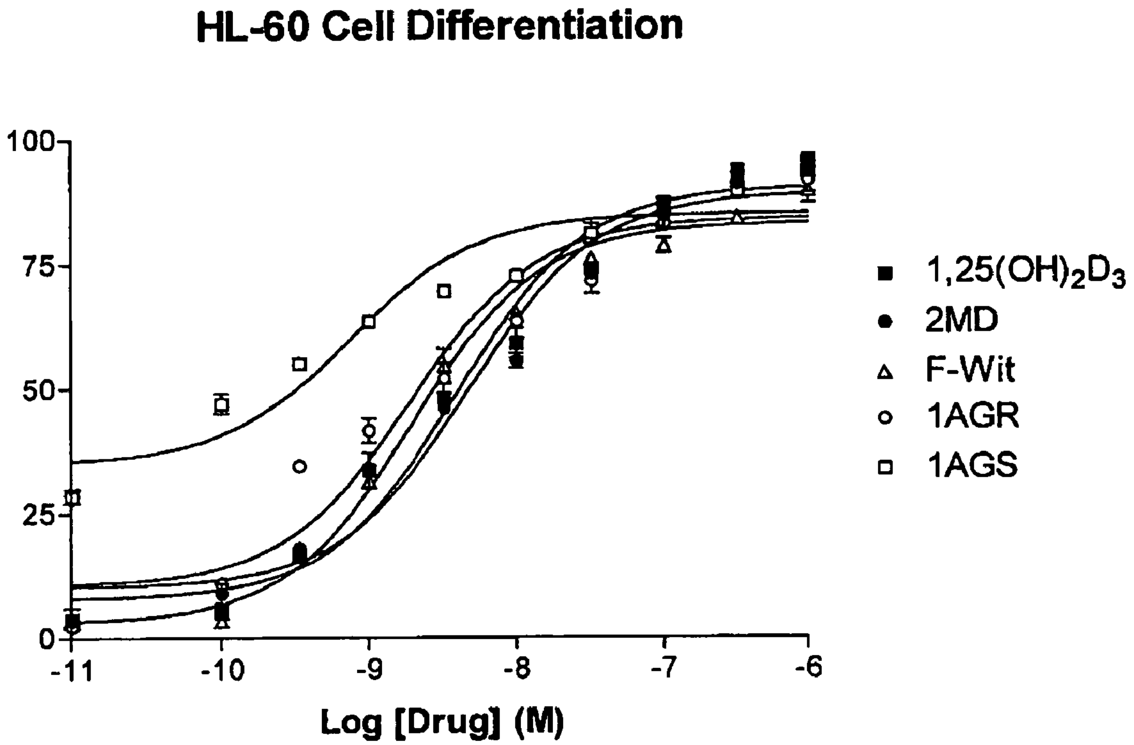

HL-60 Cell Differentiation
100
75
50
25
0
-11
-10
-9
-8
-7
-6
Log [Drug] (M)
■ 1,25(OH)$_2$D$_3$
● 2MD
△ F-Wit
○ 1AGR
□ 1AGS

Figure 3

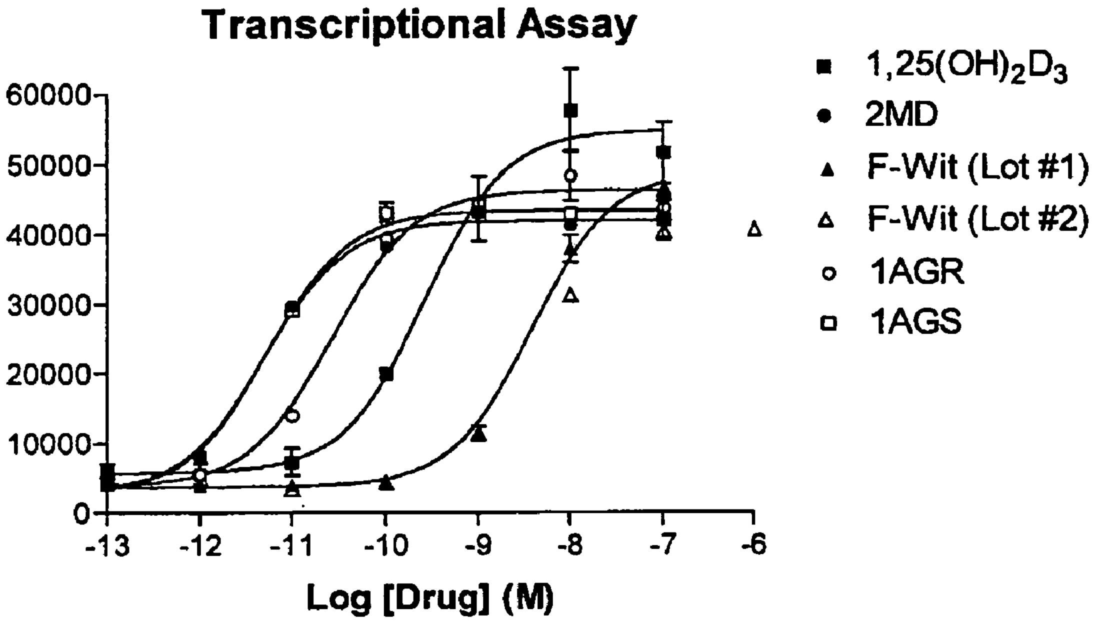

Transcriptional Assay
60000
50000
40000
30000
20000
10000
0
-13
-12
-11
-10
-9
-8
-7
-6
Log [Drug] (M)
■ 1,25(OH)2D3
● 2MD
▲ F-Wit (Lot #1)
△ F-Wit (Lot #2)
○ 1AGR
□ 1AGS

Figure 4

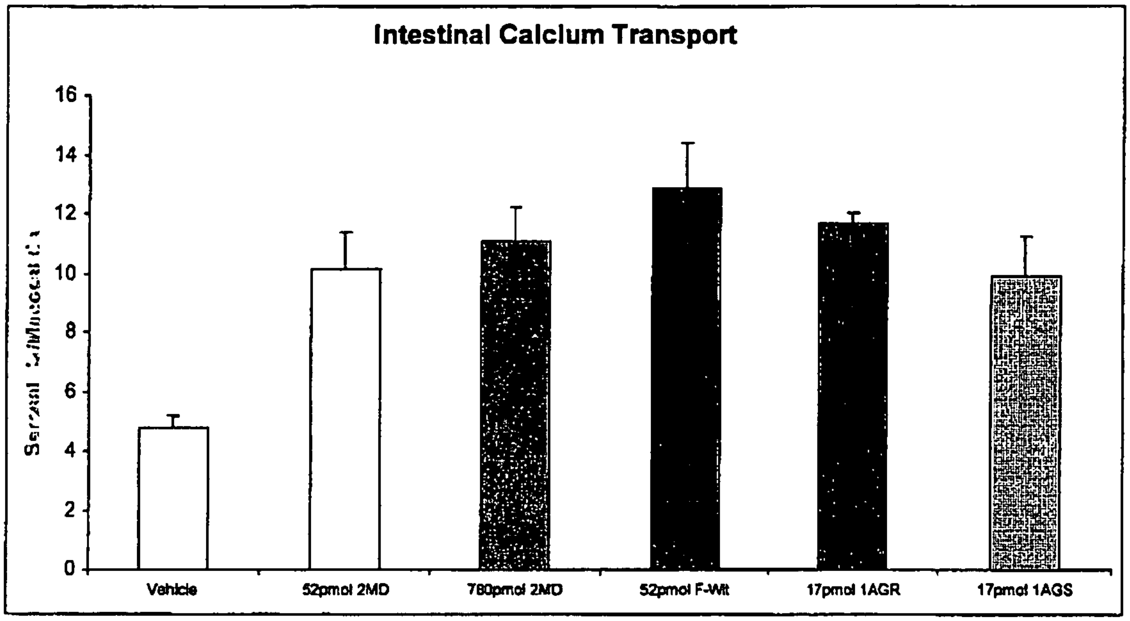

Intestinal Calcium Transport
Serosal/Mucosal Ca
0
2
4
6
8
10
12
14
16
Vehicle
52pmol 2MD
780pmol 2MD
52pmol F-Wit
17pmol 1AGR
17pmol 1AGS

Figure 5

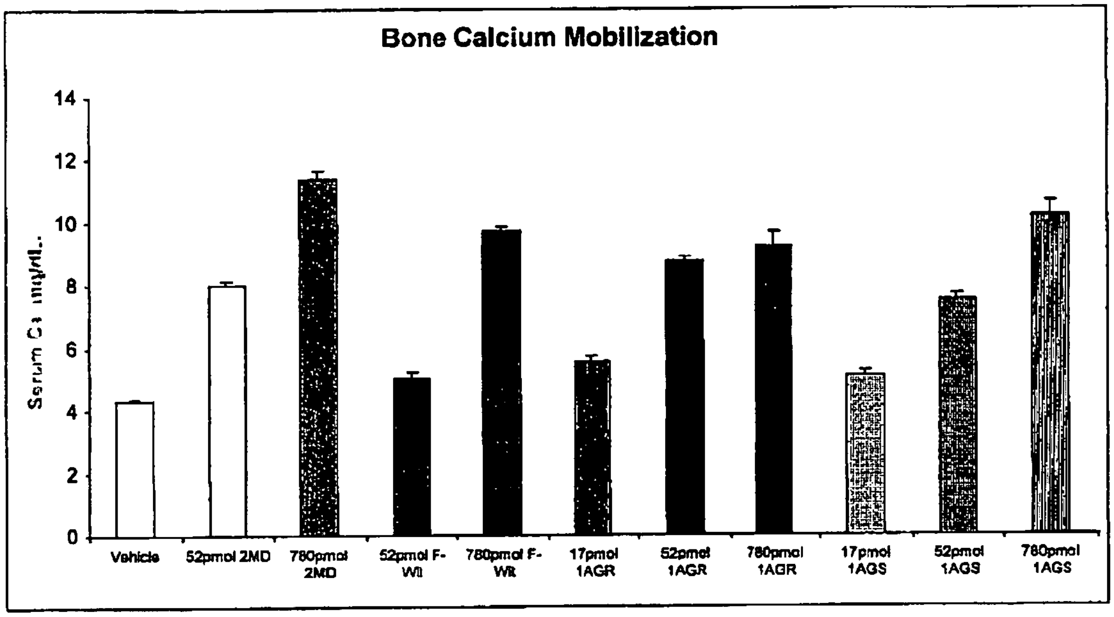

Bone Calcium Mobilization
Serum Ca mg/dL
0
2
4
6
8
10
12
14
Vehicle
52pmol 2MD
780pmol 2MD
52pmol F-Wit
780pmol F-Wit
17pmol 1AGR
52pmol 1AGR
780pmol 1AGR
17pmol 1AGS
52pmol 1AGS
780pmol 1AGS

Figure 6

2-PROPYLIDENE-19-NOR-VITAMIN D COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application No. 60/461,958, filed Apr. 10, 2003.

BACKGROUND OF THE INVENTION

The present invention relates to vitamin D compounds, and more particularly, to 2-alkylidene-19-nor-vitamin D analogs having a substituted propylidene moiety at carbon-2, pharmaceutical uses for such analogs, and a general method for chemically synthesizing such analogs.

The natural hormone 1α,25-dihydroxyvitamin D_3 and its analog in the ergosterol series, i.e. 1α,25-dihydroxyvitamin D_2 are known to be highly potent regulators of calcium homeostasis in animals and humans, and more recently their activity in cellular differentiation has been established, Ostrem et al., Proc. Natl. Acad. Sci. USA, 84, 2610 (1987). Many structural analogs of these metabolites have been prepared and tested, including 1α-hydroxyvitamin D_3, 1α-hydroxyvitamin D_2, various side chain homologated vitamins and fluorinated analogs. Some of these compounds exhibit an interesting separation of activities in cell differentiation and calcium regulation. This difference in activity may be useful in the treatment of a variety of diseases such as renal osteodystrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies.

In 1990, a new class of vitamin D analogs was discovered, i.e. the so called 19-nor-vitamin D compounds, characterized by the replacement of the ring A exocyclic methylene group (carbon 19), typical of the vitamin D system, by two hydrogen atoms. Biological testing of such 19-nor-analogs (e.g., 1α,25-dihydroxy-19-nor-vitamin D_3) revealed a selective activity profile with high potency in inducing cellular differentiation, with very low calcium mobilizing activity. Thus, these compounds are potentially useful as therapeutic agents for the treatment of malignancies, or the treatment of various skin disorders. Two different methods of synthesis of such 19-nor-vitamin D analogs have been described (Perlman et al., Tetrahedron Letters 31, 1823 (1990); Perlman et al., Tetrahedron Letters 32, 7663 (1991), and DeLuca et al., U.S. Pat. No. 5,086,191). Few years later, analogs of 1α,25-dihydroxy-19-norvitamin D_3 substituted at the 2-position of its A-ring with hydroxy or alkoxy groups (DeLuca et al., U.S. Pat. No. 5,536,713) were synthesized. It has been established that they exhibit interesting and selective activity profiles. All these studies indicate that binding sites in vitamin D receptors can accommodate different substituents at C-2 in the synthesized vitamin D analogs.

In a continuing effort to explore the 19-nor class of pharmacologically important vitamin D compounds, analogs which are characterized by the transposition of the ring A exocyclic methylene group from carbon 10 (C-10) to carbon 2 (C-2), i.e. 2-methylene-19-nor-vitamin D compounds have been recently synthesized and tested (Sicinski et al., J. Med. Chem., 41, 4662 (1998); Sicinski et al., Steroids 67, 247 (2002); DeLuca et al., U.S. Pat. Nos. 5,843,928, 5,936,133 and 6,382,071). Molecular mechanics studies, performed on these analogs, showed that a change of ring-A conformation can be expected resulting in the "flattening" of the cyclohexanediol ring. From molecular mechanics calculations and NMR studies their A-ring conformational equilibrium was established to be ca. 6:4 in

favor of the conformer that has an equatorial 1α-OH. Introduction of the 2-methylene group into 19-nor-vitamin D carbon skeleton thus changes the character of its (1α- and 3β-) A-ring hydroxyls; they are both now in the allylic positions, similarly, as the 1α-hydroxyl group (crucial for biological activity) in the molecule of the natural hormone, 1α,25-$(OH)_2D_3$. It was found that 1α,25-dihydroxy-2-methylene-19-norvitamin D analogs are characterized by significant biological potency, enhanced dramatically in compounds with "unnatural" (20S)-configuration.

Very recently, 2-ethylidene analogs of 1α,25-dihydroxy-19-norvitamin D_3 have been synthesized. Such modification of the ring A results in significant biological potency for the compounds, especially enhanced in the E-geometrical isomers, Sicinski et al., J. Med. Chem., 45, 3366 (2002). Interestingly, it has been established that E-isomers have their A-ring conformational equilibrium considerably shifted to one particular chair form, that possessing 1α-hydroxyl in an equatorial orientation.

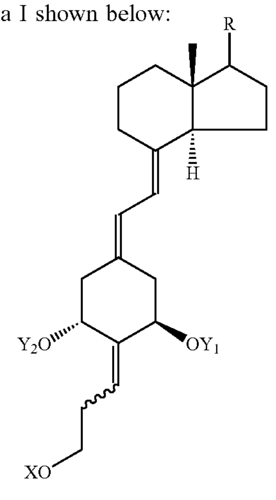
SUMMARY OF THE INVENTION

As a continuation of the search for biologically active 2-alkylidene-19-norvitamin D compounds, analogs which are characterized by the presence of substituted propylidene moiety at C-2 have now been synthesized and tested. Such vitamin D analogs seemed interesting targets because their bulky substituent at C-2 can be expected to cause an even more significant, in comparison with 2-ethylidene group, bias toward one particular A-ring chair conformation. On the other hand, the presence of an oxygen function, located at the terminus of the propylidene fragment, can introduce additional interaction with the vitamin D receptor.

A class of 1α-hydroxylated vitamin D compounds not known heretofore are the vitamin D isomers having the A-ring exocyclic methylene moiety at C-10 removed and possessing an additional fragment, being a substituted propylidene group, attached to carbon-2. Thus, the present invention is directed toward 2-alkylidene-19-nor-vitamin D analogs having a substituted propylidene moiety at carbon-2, various pharmaceutical uses for these analogs, and a general method for chemically synthesizing these analogs. In particular, the present invention is directed toward the E-isomer and Z-isomer of (20R)-1α,25-dihydroxy-2-[3'-hydroxypropylidene]-19-norvitamin D_3 as well as the E-isomer and Z-isomer of (20S)-1α,25-dihydroxy-2-[3'-hydroxypropylidene]-19-norvitamin D_3. Also disclosed is 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$.

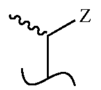
Structurally these novel analogs are characterized by the general formula I shown below:

I

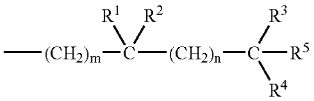


where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where X may be an alkyl, hydrogen, hydroxy-protecting group, hydroxyalkyl, alkoxyalkyl and aryloxyalkyl, and where the group R represents any of the typical side chains known for vitamin D type compounds.

More specifically, R can represent a saturated or unsaturated hydrocarbon radical of 1 to 35 carbons, that may be straight-chain, branched or cyclic and that may contain one or more additional substituents, such as hydroxy- or protected-hydroxy groups, fluoro, carbonyl, ester, epoxy, amino or other heteroatomic groups. Preferred side chains of this type are represented by the structure below



where the stereochemical center (corresponding to C-20 in steroid numbering) may have the R̲ or S̲ configuration, (i.e. either the natural configuration about carbon 20 or the 20-epi configuration), and where Z is selected from Y, —OY, —CH_2OY, —C≡CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$—(CH_2)_m—\overset{R^1\ \ R^2}{C}—(CH_2)_n—\underset{R^4}{\overset{R^3}{C}}—R^5$$

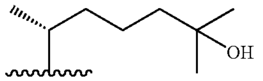
where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $═CR^2R^3$, or the group $—(CH_2)_p—$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $—(CH_2)_q—$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $—CH(CH_3)—$, $—(CH_2)_m—$, $(CH_2)_n$ or $—CR^1R^2—$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

The wavy line to the methyl substituent at carbon 20 indicates that carbon 20 may have either the R or S configuration, i.e. the natural configuration (20R) or the unnatural 20-epi configuration (20S).

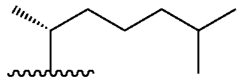
The wavy line to the carbon 1' indicates possibility of two geometrical isomers of 2-propylidene unit (differing in the orientation of substituents of terminal carbon atoms in the A-ring 1,4-dimethylenecyclohexane fragment).

Specific important examples of side chains with natural 20R-configuration are the structures represented by formulas (a), (b), (c), (d) and (e) below. i.e. the side chain as it occurs in 25-hydroxyvitamin D_3 (a); vitamin D_3 (b); 25-hydroxyvitamin D_2 (c); vitamin D_2 (d); and the C-24 epimer of 25-hydroxyvitamin D_2 (e).

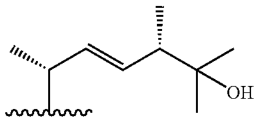
(a)



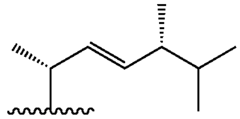
(b)



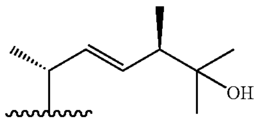
(c)



(d)



(e)



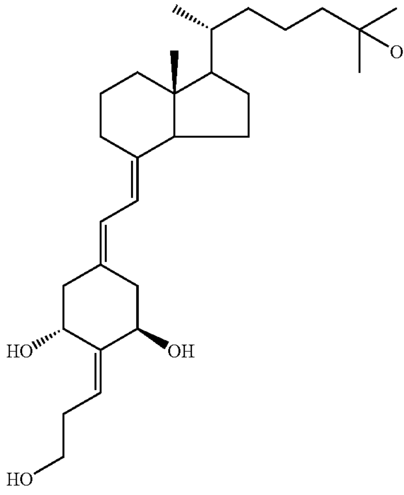
The above novel 2-propylidene-19-nor vitamin D compounds of structure I exhibit a desired, and highly advantageous, pattern of biological activity. These compounds are characterized by relatively high intestinal calcium transport activity, i.e. similar to that of 1α,25-dihydroxyvitamin D_3, while also exhibiting relatively high activity, as compared to 1α,25-dihydroxyvitamin D_3, in their ability to mobilize calcium from bone. Hence, these compounds are highly specific in their calcemic activity. Their preferential activity on intestinal calcium transport and calcium mobilizing activity allows the in vivo administration of these compounds for the treatment and prophylaxis of metabolic bone diseases where bone loss is a major concern. Because of their preferential calcemic activity on gut calcium transport and on bone, these compounds would be preferred therapeutic agents for the treatment and prophylaxis of diseases where bone formation is desired, such as osteoporosis, especially low bone turnover osteoporosis, steroid induced osteoporosis, senile osteoporosis or postmenopausal osteoporosis, as well as osteomalacia and renal osteodystrophy. The compounds may be administered transdermally, orally or parenterally. The compounds may be present in a pharmaceutical composition in an amount from about 0.01 μg/gm to about 100 μg/gm of the composition, preferably from about 0.1 μg/gm to about 50 μg/gm of the composition, and may be administered in dosages of from about 0.01 μg/day to about 100 μg/day, preferably from about 0.1 μg/day to about 50 μg/day.

The compounds of the invention are also especially suited for treatment and prophylaxis of human disorders which are characterized by an imbalance in the immune system, e.g. in autoimmune diseases, including multiple sclerosis, diabetes mellitus, lupus, host versus graft reaction, and rejection of transplants; and additionally for the treatment and prophylaxis of inflammatory diseases, such as rheumatoid arthritis, asthma, and inflammatory bowel diseases such as Crohn's disease or ulcerative colitis, as well as the improvement of bone fracture healing and improved bone grafts. It has also been discovered that these compounds increase breaking strength (cortical strength) as well as crushing strength (trabecular strength) of bones. Thus, these compounds could also be used in conjunction with bone replacement procedures such as hip replacements, knee replacements, and the like. Acne, alopecia, skin conditions such as dry skin (lack of dermal hydration), undue skin slackness (insufficient skin firmness), insufficient sebum secretion and wrinkles, and hypertension are other conditions which may be treated with the compounds of the invention.

The above compounds are also characterized by high cell differentiation activity. Thus, these compounds also provide therapeutic agents for the treatment of psoriasis, or as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer. The compounds may be present in a composition to treat psoriasis in an amount from about 0.01 μg/gm to about 100 μg/gm of the composition, preferably from about 0.1 μg/gm to about 50 μg/gm of the composition, and may be administered topically, transdermally, orally or parenterally in dosages of from about 0.01 μg/day to about 100 μg/day, preferably from about 0.1 μg/day to about 50 μg/day.

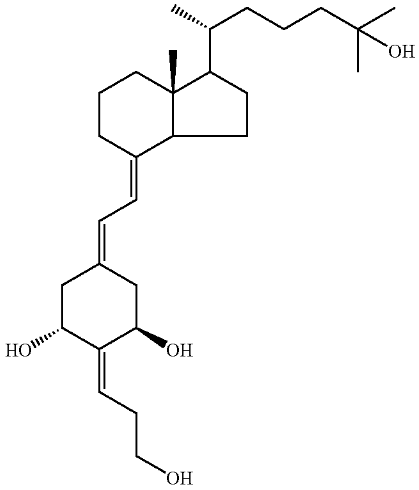
In particular, the E-isomer and Z-isomer of both the (20R) and (20S) isomers of 1α,25-dihydroxy-2-[3'-hydroxypropylidene]-19-norvitamin D_3 have been synthesized and their binding, transcriptional, calcemic (both intestinal calcium transport and bone calcium mobilization) and differentiation activities determined. Structurally, the E-isomer of this (20R) analog is characterized by the general formula Ia shown below and is referred to herein as "1AGR":

Ia



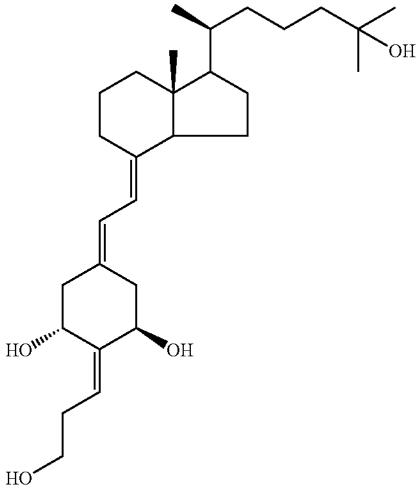
Structurally, the Z-isomer of this (20R) analog is characterized by the general formula Ib shown below and is referred to herein as "2AGR":

Ib



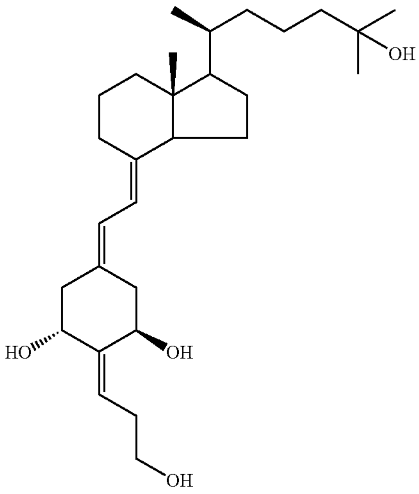
Structurally, the E-isomer of this (20S) analog is characterized by the general formula Ic shown below and is referred to herein as "1AGS":

Ic



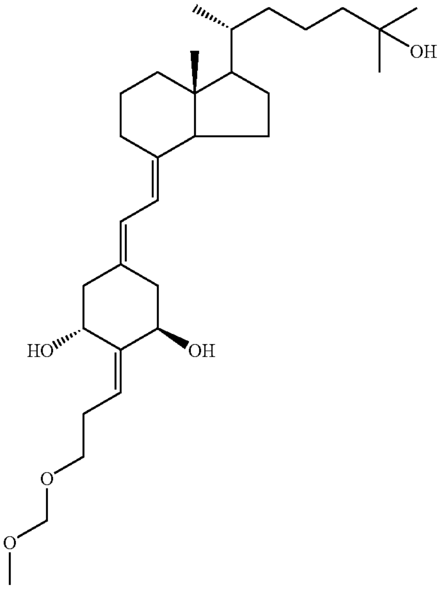
Structurally, the Z-isomer of this (20S) analog is characterized by the general formula Id shown below and is referred to herein as "2AGS":

Id



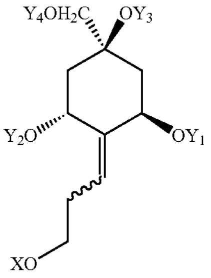
Another 2-propylidene compound that has been synthesized is 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α, 25-dihydroxyvitamin D_3, and its binding, transcriptional, calcemic (both intestinal calcium transport, and bone calcium mobilization) and differentiation activities were determined. Structurally, this analog is characterized by the general formula Ie shown below, and is referred to herein as "F-Wit":

Ie



The invention also provides a novel synthesis for the production of the end products of formula I, and specifically of formulae Ia through Id. In addition, this invention provides novel intermediate compounds formed during the synthesis of the end products. Structurally, these novel intermediates are characterized by the general formulae V, VI, VII, VIII, IX and X below where Y_1, Y_2, Y_3, and Y_4, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, and X may be an alkyl, hydrogen, hydroxy-protecting group, hydroxyalkyl, alkoxyalkyl and aryloxyalkyl.

V



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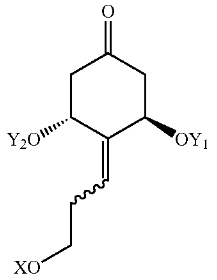
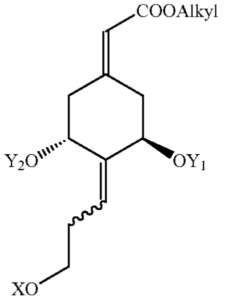
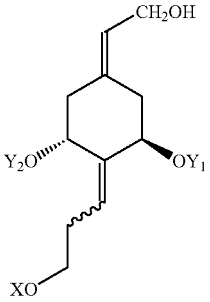
VI



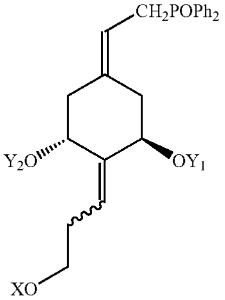
VII



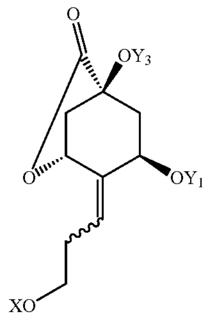
VIII



IX



X



BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph illustrating the relative activity of 1α,25-dihydroxyvitamin D_3 as well as the herein described and claimed 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$ (F-Wit) in binding to the 1α,25-dihydroxyvitamin D pig intestinal nuclear receptor;

FIG. **2** is a graph illustrating the relative activity of 1α,25-dihydroxyvitamin D_3 as well as the herein described and claimed E-isomer of 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (1AGR), the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2D_3$ (1AGS), the Z-isomer of 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (2AGR), and the Z-isomer of 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (2AGS);

FIG. **3** is a graph illustrating the percent BL-60 cell differentiation as a function of the concentration of 1α,25-dihydroxyvitamin D_3, (20S)-2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 (2MD) and the herein desribed and claimed 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$ (F-Wit), the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (1AGR), and the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2D_3$ (1AGS);

FIG. **4** is a graph illustrating the transcriptional activity as a function of the concentration of 1α,25-dihydroxyvitamin, (20S)-2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 (2MD) and the herein described and claimed 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$ (F-Wit), the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (1AGR), and the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2D_3$ (1AGS);

FIG. **5** is a bar graph illustrating the intestinal calcium transport activity of 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$ (F-Wit), the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (1AGR), and the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2D_3$ (1AGS) at various dosages as compared to control (vehicle) and (20S)-2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 (2MD); and

FIG. **6** is a bar graph illustrating the bone calcium mobilization activity of 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$ (F-Wit), the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (1AGR), and the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2D_3$ (1AGS) at various dosages as compared to control (vehicle) and (20S)-2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 (2MD).

DETAILED DESCRIPTION OF THE INVENTION

As used in the description and in the claims, the term "hydroxy-protecting group" signifies any group commonly used for the temporary protection of hydroxy functions, such as for example, alkoxycarbonyl, acyl, alkylsilyl or alkylarylsilyl groups (hereinafter referred to simply as "silyl" groups), and alkoxyalkyl groups. Alkoxycarbonyl protecting groups are alkyl-O—CO— groupings such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or allyloxycarbonyl. The term "acyl" signifies an alkanoyl group of 1 to 6 carbons, in all of its isomeric forms, or a carboxyalkanoyl group of 1 to 6 carbons, such as an oxalyl, malonyl, succinyl, glutaryl group, or an aromatic acyl group such as benzoyl, or a halo, nitro or alkyl substituted benzoyl group. The word "alkyl" as used in the description or the claims, denotes a straight-chain or branched alkyl radical of 1 to 10 carbons, in all its isomeric forms. Alkoxyalkyl protecting groups are groupings such as methoxymethyl, ethoxymethyl, methoxyethoxymethyl, or tetrahydrofuranyl and tetrahydropyranyl. Preferred silyl-protecting groups are trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, dibutylmethylsilyl, diphenylmethylsilyl, phenyldimethylsilyl, diphenyl-t-butylsilyl and analogous alkylated silyl radicals. The term "aryl" specifies a phenyl-, or an alkyl-, nitro- or halo-substituted phenyl group.

A "protected hydroxy" group is a hydroxy group derivatised or protected by any of the above groups commonly used for the temporary or permanent protection of hydroxy functions, e.g. the silyl, alkoxyalkyl, acyl or alkoxycarbonyl groups, as previously defined. The terms "hydroxyalkyl", "deuteroalkyl" and "fluoroalkyl" refer to an alkyl radical substituted by one or more hydroxy, deuterium or fluoro groups respectively.

It should be noted in this description that the term "24-homo" refers to the addition of one methylene group and the term "24-dihomo" refers to the addition of two methylene groups at the carbon 24 position in the side chain. Likewise, the term "trihomo" refers to the addition of three methylene groups. Also, the term "26,27-dimethyl" refers to the addition of a methyl group at the carbon 26 and 27 positions so that for example R^3 and R^4 are ethyl groups. Likewise, the term "26,27-diethyl" refers to the addition of an ethyl group at the 26 and 27 positions so that R^3 and R^4 are propyl groups.

In the following lists of side chain unsaturated and side chain saturated compounds, if the methyl group attached at the carbon 20 position is in its epi or unnatural configuration, the term "20(S)" or "20-epi" should be included in each of the following named compounds. Also, if the side chain contains an oxygen atom substituted at any of positions 20, 22 or 23, the term "20-oxa," "22-oxa" or "23-oxa," respectively, should be added to the named compound. The named compounds could also be of the vitamin D_2 type if desired.

Specific and preferred examples of the 2-propylidene-19-nor-vitamin D compounds of structure I when the side chain is unsaturated are:

2-(3'-hydroxypropylidene)-19-nor-1α-hydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-25-hydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-1α,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-dimethyl-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-dimethyl-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-dimethyl-24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-diethyl-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-diethyl-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-diethyl-24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-dipropyl-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-dipropyl-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3; and

2-(3'-hydroxypropylidene)-19-nor-26,27-dipropyl-24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3.

With respect to the above unsaturated compounds, it should be noted that the double bond located between the 22 and 23 carbon atoms in the side chain may be in either the (E) or (Z) configuration. Accordingly, depending upon the configuration, the term “22,23(E)” or “22,23(Z)” could be included in each of the above named compounds. Also, it is common to designate the double bond located between the 22 and 23 carbon atoms with the designation “Δ^{22}”. Thus, for example, the fourth named compound above could also be written as 2-(3'-hydroxypropylidene)-19-nor-24-homo-22,23(E)-Δ^{22}-1,25-$(OH)_2D_3$ where the double bond is the (E) configuration. Similarly, if the methyl group attached at carbon 20 is in the unnatural configuration, this compound could be written as 2-(3'-hydroxypropylidene)-19-nor-20(S)-24-homo-22,23(E)-Δ^{22}-1,25-$(OH)_2D_3$.

Specific and preferred examples of the 2-propylidene-19-nor-vitamin D compounds of structure I when the side chain is saturated are:

2-(3'-hydroxypropylidene)-19-nor-1α-hydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-25-hydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-1α,25-dihydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-24-homo-1,25-dihydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-24-dihomo-1,25-dihydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-24-trihomo-1,25-dihydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-dimethyl-24-homo-1,25-dihydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-dimethyl-24-dihomo-1,25-dihydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-dimethyl-24-trihomo-1,25-dihydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-diethyl-24-homo-1,25-dihydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-diethyl-24-dihomo-1,25-dihydroxyvitamin D_3;

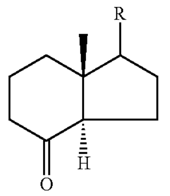
2-(3'-hydroxypropylidene)-19-nor-26,27-diethyl-24-trihomo-1,25-dihydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-dipropyl-24-homo-1,25-dihydroxyvitamin D_3;

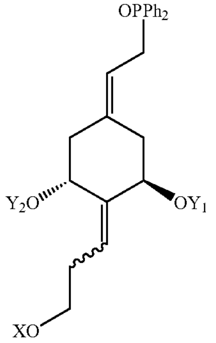
2-(3'-hydroxypropylidene)-19-nor-26,27-dipropyl-24-dihomo-1,25-dihydroxyvitamin D_3;

2-(3'-hydroxypropylidene)-19-nor-26,27-dipropyl-24-trihomo-1,25-dihydroxyvitamin D_3;

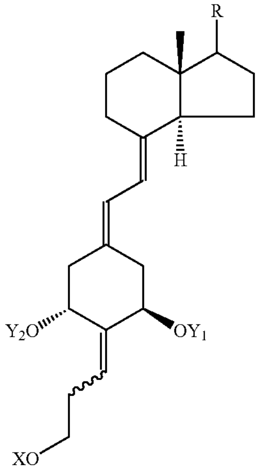
The preparation of 1α-hydroxy-19-nor-vitamin D compounds, with the substituted propylidene moiety at C-2, of the basic structure I can be accomplished by a common general method, i.e. the condensation of a bicyclic Windaus-Grundmann type ketone II with the allylic phosphine oxide III to the corresponding hydroxy-protected vitamin D analog IV followed by deprotection at C-1 and C-3.



II



III



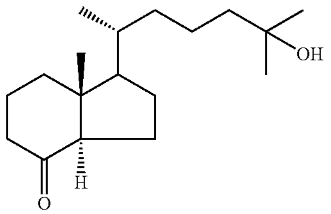
IV

In the structures II and III, groups Y_1, Y_2, X and R represent groups defined above; Y_1, Y_2, and X preferably hydroxy-protecting groups, it being also understood that any functionalities in R that might be sensitive, or that interfere with the condensation reaction, be suitable protected as is well-known in the art. The process shown above represents an application of the convergent synthesis concept, which has been applied effectively for the preparation of vitamin D compounds (e.g. Lythgoe et al., J. Chem. Soc. Perkin Trans. I, 590 (1978); Lythgoe, Chem. Soc. Rev. 9, 449 (1983); Toh et al., J. Org. Chem. 48, 1414 (1983); Baggiolini et al., J. Org. Chem. 51, 3098 (1986); Sardina et al., J. Org. Chem. 51, 1264 (1986); J. Org. Chem. 51, 1269 (1986); DeLuca et al., U.S. Pat. No. 5,086,191; DeLuca et al., U.S. Pat. No. 5,536,713).

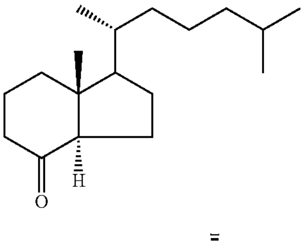
Hydrindanones of the general structure II are known, or can be prepared by known methods. Specific important examples of such known bicyclic ketones are the structures with the side chains (a), (b), (c) and (d) described above, i.e. 25-hydroxy Grundmann's ketone (e) [Baggiolini et al., J. Org. Chem, 51, 3098 (1986)]; Grundmann's ketone (f) [Inhoffen et al., Chem. Ber. 90, 664 (1957)]; 25-hydroxy

Windaus ketone (g) [Baggiolini et al., J. Org. Chem, 51, 3098 (1986)]and Windaus ketone (h) [Windaus et al., Ann., 524, 297 (1936)]:

(e)



(f)



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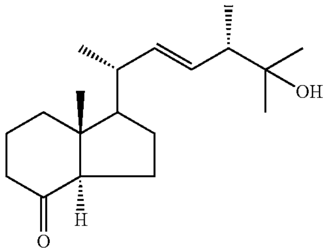
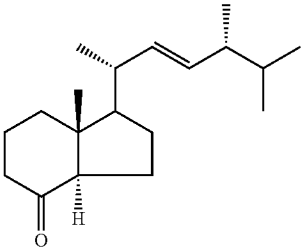


(h)



For the preparation of the required phosphine oxides of general structure III, a new synthetic route has been developed starting from bicyclic lactone 1 that was obtained from commercial (1R,3R,4S,5R)-(−)-quinic acid as described previously [Hanessian et al., J. Org. Chem. 62, 465 (1997)]. The overall process of transformation of the starting lactone 1 into the desired A-ring synthons, is summarized by the SCHEME I. Thus, one of the two secondary hydroxy groups of 1 (equatorial hydroxyl at C-3) was selectively protected as t-butyldimethylsilyl ether (TBDMS) and the other was then oxidized with Dess-Martin periodinane reagent to the 4-ketone 3. The tertiary 1-hydroxyl was acetylated and the resulted acetoxy ketone 4 subjected to the Wittig reaction with an ylide generated from the appropriate phosphonium salt. The choice of the phosphonium salt used for this purpose should be made considering the structure of the final 19-norvitamin D. In the case of the attempted synthesis of the 19-norvitamin D analog with the 2-propylidene moiety substituted at the terminal carbon with some functional group other than hydroxyl it might be desirable to use introduce such propylidene fragment to the carbon 4 of the keto compound 4. Such situation is exemplified in the experimental part as EXAMPLE I where the synthesis of 1α,25-dihydroxy-2-[3'-(methoxymethoxy)-propylidene]-19-norvitamin D_3 (21) is described. In the case of attempted preparation 1α,25-dihydroxy-2-(3'-hydroxypropylidene)-19-norvitamin D analogs it might be desirable to attach protected 3-hydroxypropylidene fragment to C-4 in the compound 4. Such situation is exemplified in the experimental part as EXAMPLE II where the synthesis of both E- and Z-geometrical isomers of 1α,25-dihydroxy-2-(3'-hydroxypropylidene)-19-norvitamin D_3 (24a,b) and their 20S-counterparts (25a,b) is described. The phosphonium salts A and B, used in these processes, were prepared from 3-bromo-1-propanol. Thus, in the first synthesis the Wittig reaction of the keto lactone 4 with ylide generated from phosphonium bromide A and n-butyllithium afforded two isomeric olefinic compounds 5a and 5b in the ratio of ca. 5:1. Simultaneous reduction of the lactone ring and acetate group in the major compound 5a with sodium borohydride or other suitable reducing agent (e.g. lithium aluminum hydride) provided the triol 7 (SCHEME II) which was subsequently oxidized by sodium periodate to the cyclohexanone derivative 9. The next steps of the process comprise protection of the secondary hydroxyl as TBDMS ether and subsequent Peterson reaction of the ketone 11 with methyl(trimethylsilyl)acetate. The resulting mixture of the allylic esters 13a and 13b (ratio of isomers ca. 7:1) was treated with DIBALH or other suitable reducing agent (e.g. lithium aluminum hydride) and the formed allylic alcohols 15a and 15b were then transformed to the desired A-ring phosphine oxides 17a and 17b. This last transformation involved 3 steps, namely, in situ tosylation with n-butyllithium and p-toluenesulfonyl chloride, followed by reaction with diphenylphosphine lithium salt and oxidation with hydrogen peroxide. Alternatively, in the second synthesis the Wittig reaction of the keto lactone 4 was performed with ylide generated from phosphonium bromide B and it afforded two isomeric olefins 6a and 6b in the ratio of ca. 3:2. Reduction and periodate oxidation followed by silylation provided the corresponding keto compound 12. Subsequent Peterson reaction gave a mixture of the allylic esters 14a and 14b (ratio of isomers ca. 6:1) which was converted to the respective phosphine oxides 18a and 18b.

Several 2-methylene-19-nor-vitamin D compounds may be synthesized using the A-ring synthons 17a,b and 18a,b and the appropriate Windaus-Grundmann ketones having the desired side chain structure. Thus, for example, Wittig-Horner coupling of the lithium phosphinoxy carbanion generated from 17a and phenyllithium with the protected 25-hydroxy Grundmann's ketone 19a (SCHEME III), prepared according to published procedure [Sicinski et al., J. Med. Chem. 37, 3730 (1994)], gave the expected protected vitamin compound 20. This, after deprotection with tetrabutylammonium fluoride afforded 1α,25-dihydroxy-2-[3'-(methoxymethoxy)-propylidene]-19-norvitamin D_3 (21). Alternatively, Wittig-Horner reaction of the anion generated from 18a,b and phenyllithium with the protected 25-hydroxy Grundmann's ketone 19a, provided after hydroxyls deprotection the expected E- and Z-isomers of 1α,25-dihydroxy-2-(3'-hydroxypropylidene)-19-norvitamin D_3 (24a,b), whereas coupling of the phosphine oxides 18a,b with the (20S)-Grundmann's ketone derivative 19b and subsequent hydrolysis resulted in formation of the corresponding E- and Z-isomers of (20S)-1α,25-dihydroxy-2-(3'-hydroxypropylidene)-19-nor-vitamin D_3 (25a,b).

As noted above, other 19-nor-vitamin D analogs may be synthesized by the method disclosed herein.

This invention is described by the following illustrative examples. In these examples specific products identified by

Arabic numerals (e.g. 1, 2, 3, etc) refer to the specific structures so identified in the preceding description and in the SCHEME I, SCHEME II, and SCHEME III.

EXAMPLES

Chemistry. Melting points (uncorrected) were determined on a Thomas-Hoover capillary melting-point apparatus. Ultraviolet (UV) absorption spectra were recorded with a Perkin-Elmer Lambda 3B UV-VIS spectrophotometer in ethanol. ^1H nuclear magnetic resonance (NMR) spectra were recorded at 400 and 500 MHz with a Bruker Instruments DMX-400 and DMX-500 Avance console spectrometers in deteriochloroform. ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 125 MHz with a Bruker Instruments DMX-500 Avance console spectrometer in deuteriochloroform. Chemical shifts (δ) are reported downfield from internal Me_4Si (δ 0.00). Electron impact (EI) mass spectra were obtained with a Micromass AutoSpec (Beverly, Mass.) instrument. High-performance liquid chromatography (HPLC) was performed on a Waters Associates liquid chromatograph equipped with a Model 6000A solvent delivery system, a Model U6K Universal injector, and a Model 486 tunable absorbance detector. THF was freshly distilled before use from sodium benzophenone ketyl under argon.

Example I

Preparation of 1α,25-dihydroxy-2-[3'-(methoxymethoxy)propylidene]-19-norvitamin D_3

Referring first to SCHEME I the starting bicyclic lactone 1 was obtained from commercial (−)-quinic acid as described previously [Hanessian et al., J. Org. Chem. 62, 465 (1997)].

(a) Protection of 3-Hydroxy Group in the Lactone 1. (1R,3R,4S,5SR)-1,4-Dihydroxy-3-[(tert-butyldimethylsilyl)oxy]-6-oxa-bicyclo[3.2.1]octan-7-one (2). To a stirred solution of lactone 1 (1.80 g, 10.34 mmol) and imidazole (2.63 g, 38.2 mmol) in anhydrous DMF (14 mL) was added t-butyldimethylsilyl chloride (1.80 g, 11.9 mmol) at 0° C. The mixture was stirred at 0° C. for 30 min and 1 h at room temperature, poured into water and extracted with ethyl acetate and ether. The organic layer was washed several times with water, dried ($MgSO_4$), and evaporated to give a colorless crystalline residue which was crystallized from hexane/ethyl acetate to give 2.12 g of pure 2. The mother liquors were evaporated and purified by flash chromatography. Elution with hexane/ethyl acetate (8:2) gave additional quantity of crystalline monoether 2 (0.14 g, overall yield 76%) and some quantity of crystalline isomeric (3—OH, 4-OTBDMS) ether (0.10 g, 3%). 2: m.p. 90-94° C. (from hexane); $[\alpha]^{24}_D$−44° (c 1.00 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.095 (6H, s, 2×$SiCH_3$), 0.901 (9H, s, Si-t-Bu), ca. 2.0 (2H, br m, 2α- and 2β-H), 2.29 (1H, ddd, J=11.6, 6.0, 2.6 Hz, 8β-H), 2.63 (1H, d, J=11.6 Hz, 8α-H), 3.89 (1H, ddd, J=10.4, 7.0, 4.5 Hz, 3β-H), 3.98 (1H, t, J=4.6 Hz, 41-H), 4.88 (1H, dd, J=6.0, 4.8 Hz, 5α-H); ^{13}C NMR (125 MHz) δ -5.0 (Si—CH_3), −4.7 (Si—CH_3), 17.9 $[\underline{C}(CH_3)_3]$, 25.6 $[C(\underline{C}H_3)_3]$, 36.4 (C_8), 40.2 (C_2), 65.8 (C_4), 67.0 (C_3), 71.9 (C_1), 76.3 (C_5), 177.9 (C═O), MS (EI) m/z (relative intensity) 288 (M^+, 1), 231 (41), 213 (21), 185 (85), 75 (100); HRMS (ESI), exact mass calcd for $C_{13}H_{24}O_5SiNa$ (M^++Na) 311.1291, measured 311.1287; Anal. Calcd for $C_{13}H_{24}O_5Si$: C, 54.14, H, 8.39. Found: C, 53.94, H, 8.36.

(b) Oxidation of 4-Hydroxy Group in the Dihydroxy Lactone 2.

(1R,3R,5R)-3-[(tert-Butyldimethylsilyl)oxy]-1-hydroxy-6-oxa-bicyclo[3.2.1]octane-4,7-dione (3). To a stirred suspension of Dess-Martin periodinane reagent (6.60 g, 15.5 mmol) in anhydrous CH_2Cl_2 (100 mL) was added compound 2 (3.86 g, 13.4 mmol). The mixture was stirred at room temperature for 18 h, poured into water and extracted with ethyl acetate. The organic layer was washed several times with water, dried ($MgSO_4$), and evaporated to give an oily residue which slowly crystallized on cooling (3.67 g, 95%). TLC indicated high purity of the obtained ketone 3 which could be used in the next step without further purification. Analytical sample was obtained by recrystallization from hexane. 3: m.p. 92-95° C.; ^1H NMR (400 MHz, $CDCl_3$) δ 0.040 and 0.133 (3H and 3H, each s, 2×$SiCH_3$), 0.895 (9H, s, Si-t-Bu), 2.15 (1H, dd, J=12.4, 10,4 Hz, 2α-H), 2.42 (1H, d, J=12.5 Hz, 8α-H), 2.54 (1H, ddd, J=12.4, 9.0, 3.9 Hz, 2β-H), 2.86 (1H, ddd, J=12.5, 6.7, 3.9 Hz, 8β-H), 4.54 (1H, dd, J=10.4, 9.0 Hz, 3β-H), 4.73 (1H, d, J=6.7 Hz, 5α-H); ^{13}C NMR (125 MHz) δ −5.6 (Si—CH_3), −4.8 (Si—CH_3), 18.2 $[\underline{C}(CH_3)_3]$, 25.6 $[C(\underline{C}H_3)_3]$, 42.3 (C_8), 43.0 (C_2), 70.3 (C_3), 71.8 (C_1), 78.7 (C_5), 177.1 (C═O), 202.4 (C_4); MS (EI) m/z (relative intensity) no M^+, 271 (M^+—CH_3, 4), 229 (92), 201 (28), 157 (100); HRMS (ESI) exact mass calcd for $C_9H_{13}O_5Si$ (M^+-t-Bu) 229.0532, measured 229.0539; Anal. Calcd for $C_{13}H_{22}O_5Si$×H_2O: C, 51.29, H, 7.95. Found: C, 51.09, H, 7.90.

(c) Acetylation of 1-Hydroxy Group in the Hydroxy Ketone 3.

(1R,3R,5R)-1-Acetoxy-3-[(tert-butyldimethylsilyl)oxy]-6-oxa-bicyclo[3.2.1]octane-4,7-dione (4). Solution of hydroxy ketone 3 (1.64 g, 5.8 mmol) in anhydrous pyridine (12 mL) and acetic anhydride (5.5 mL) was stirred for 3 h at room temperature. It was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, saturated $CuSO_4$ and water, dried ($MgSO_4$), and evaporated to give an oily residue which was dissolved in hexane/ethyl acetate (8:2) and filtered through short path of silica gel. Evaporation of solvents gave pure crystalline acetate 4 (1.51 g, 81%). Analytical sample was obtained by recrystallization from hexane/ethyl acetate. 4: m.p. 134-7° C.; $[\alpha]^{24}_D$−78° (c 1.00 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.046 and 0.141 (3H and 3H, each s, 2×$SiCH_3$), 0.901 (9H, s, Si-t-Bu), 2.17 (3H, s, CH_3CO), 2.28 (1H, dd, J=12.2, 10.4 Hz, 2α-H), 2.32 (1H, d, J=12.1 Hz, 8α-H), 2.65 (1H, ddd, J=12.2, 8.8, 3.9 Hz, 2β-H), 3.56 (1H, ddd , J=12.1, 6.9, 3.9 Hz, 8β-H), 4.58 (1H, dd, J=10.4, 8.8 Hz, 3β-H), 4.80 (1H, d, J=6.9 Hz, 5α-H); ^{13}C NMR (125 MHz) δ −5.8 (Si—CH_3), −4.9 (Si—CH_3), 18.2 $[\underline{C}(CH_3)_3]$, 20.9 ($\underline{C}H_3$—C═O), 25.6 $[C(\underline{C}H_3)_3]$, 38.3 (C_8), 40.3 (C_2), 70.4 (C_3), 75.3 (C_1), 78.4 (C_5), 169.1 (CH_3—C═O), 171.5 (C═O), 201.8 (C_4); MS (EI) m/z (relative intensity) 328 (M^+, 6), 271 (100), 256 (38), 229 (54), 211 (53); HRMS (ESI) exact mass calcd for $C_{11}H_{15}O_6Si$ (M^+-t-Bu) 271.0638, measured 271.0646; Anal. Calcd for $C_{15}H_{24}O_6Si$: C, 54.86, H, 7.37. Found: C, 54.88, H, 7.37.

(d) Preparation of the Phosphonium Bromide A.

[3-(Methoxymethoxy)propyl]triphenylphosphonium bromide (A). To a solution of bromomethyl methyl ether (1.3 mL, 16 mmol) and N,N-diisopropylethylamine (4.5 mL, 27.7 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0° C. was added 3-bromo-1-propanol (1.0 mL, 11 mmol) and the mixture was stirred at 0° C. for 1 h and at room temperature for 20 h. The reaction mixture was poured into 1 N HCl (150 mnL), organic phase was separated and water phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and diluted $NaHCO_3$, dried ($MgSO_4$), and evaporated to give a yellowish oil. The residue was purified by flash chromatography. Elution with hexane/ethyl acetate (95:5) afforded pure oily 1-bromo-3-(methoxymethoxy)propane (1.12 g, 55%): ^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (2H, m, $CH_2—C\underline{H}_2—CH_2$), 3.37 (3H, s, $O—CH_3$), 3.53 (2H, br t, J=6.5 Hz, $Br—CH_2$), 3.67 (2H, br t, J=5.8 Hz, $CH_2—C\underline{H}_2—O$), 4.63 (2H, s, $O—CH_2—O$).

To a solution of 1-bromo-3-(methoxymethoxy)propane (0.46 g, 2.5 mmol) in anhydrous toluene (1.5 mL) was added triphenylphoshine (0.71 g, 2.7 mmol) under argon with stirring. The mixture was heated at 100° C. for 20 h and cooled to room temperature. The liquid was decanted and the solid residue was grounded with spatula, filtered and washed several times with ether. After drying overnight in vacuum dessicator colorless crystals of phosphonium salt A (0.98 g, 88%) could be used in the Wittig reaction without further purification. A: ^1H NMR (500 MHz, $CDCl_3$) δ 1.96 (2H, m, $CH_2—C\underline{H}_2—CH_2$), 3.31 (3H, s, $O—CH_3$), 3.85 (2H, br t, J=5.6 Hz, $CH_2—C\underline{H}_2—O$), 4.00 (2H, m, $P—CH_2$), 4.60 (2H, s, $O—CH_2—O$), 7.70, 7.79 and 7.86 (6H, 3H and 6H, each m, Ar—H); Anal. Calcd for $C_{23}H_{26}O_2PBr$: C, 62.03, H, 5.88, Br, 17.94. Found: C, 61.87, H, 5.77, Br, 17.89.

(e) Wittig Reaction of the 4-Ketone 4 with the ylide generated from A.

[(E)- and (Z)-(1R,3R,5R)-1-Acetoxy-3-[(tert-butyldimethylsilyl)oxy]-6-oxa-4-[3'-(methoxymethoxy)propylidene] bicyclo[3.2.1]octan-7-one (5a and 5b). To the phoshonium bromide A (420 mg, 0.94 mmol) in anhydrous THF (5 mL) at 0° C. was added dropwise n-BuLi (1.6 M in hexanes, 1.12 mL, 1.8 mmol) under argon with stirring. After 5 min another portion of A was added (420 mg, 0.94 mmol) and the solution was stirred at 0° C. for 10 min and then at room temperature for 20 min. The orange-red mixture was cooled to −78° C. and siphoned in 2 equal portions (30 min interval) to a solution of keto lactone 4 (300 mg, 0.91 mmol) in anhydrous THF (8 mL). The reaction mixture was stirred at −78° C. and stopped by addition of brine cont. 1% HCl (3 h after addition of the first portion of the Wittig reagent). Ethyl acetate (9 mL), benzene (6 mL), ether (3 mL), sat. $NaHCO_3$ (3 mL), and water (3 ml) were added and the mixture was vigorously stirred at room temperature for 18 h. Then an organic phase was separated, washed with brine, dried ($MgSO_4$), and evaporated. The oily residue (consisting mainly with isomeric 5a and 5b in the ratio of ca. 5:1) was separated by flash chromatography on silica. Elution with hexane/ethyl acetate (85:15) resulted in partial separation of products: 29 mg of 5b, mixture of 5a and 5b (85 mg) and pure 5a (176 mg; total yield 77%). Rechromatography of the mixed fractions resulted in almost complete separation of the products 5a: $[\alpha]^{24}_D$−63° (c 0.60 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.074 (6H, s, $2\times SiCH_3$), 0.914 (9H, s, Si-t-Bu), 2.13 (3H, s, OCH_3), 2.00 (1H, br t, J=11.2, Hz, 2α-H), 2.10 (1H, d, J=10.8 Hz, 8α-H), 2.34 (1H, ddd, J=11.7, 7.0, 2.9 Hz, 2β-H), 2.38 and 2.43 (1H and 1H, each m, $=C—CH_2$), 3.31 (1H, ddd, J=10.8, 6.5, 2.9 Hz, 8β-H), 3.35 (3H, s, $O—CH_3$), 3.54 and 3.60 (1H and 1H, each m, $CH_2—C\underline{H}_2—O$), 4.41 (1H, t, J=8.2 Hz, 3β-H), 4.60 (2H, s, $O—CH_2—O$), 5.52 (1H, d, J=6.5 Hz, 5α-H), 5.71 (1H, br t, J=7.1 Hz, =CH); ^{13}C NMR (125 MHz) δ −5.1 ($Si—CH_3$), −4.9 ($Si—CH_3$), 18.1 [$\underline{C}(CH_3)_3$], 21.1 $\underline{C}H_3—C=O$), 25.7 [$C(\underline{C}H_3)_3$], 27.5 ($CH_2—C\underline{H}_2—C=$), 40.5 (C_8), 41.5 (C_2), 55.2 ($O—CH_3$), 66.7 ($O—\underline{C}H_2—CH_2$), 66.8 (C_3), 77.1 (C_1), 73.9 (C_5), 96.3 ($O—CH_2—O$), 121.9 ($=\underline{C}—CH_2$), 136.8 (C_4), 169.1 ($CH_3—\underline{C}=O$), 172.9 (C=O); MS (EI) m/z (relative intensity), no M^+, 383 (M^+−OCH_3, 3), 357 (10), 325 (44), 297 (12), 267 (15), 265 (40), 237 (89), 75 (100); HRMS (ESI) exact mass calcd for $C_{20}H_{34}O_7SiNa$ (M^++Na) 437.1972, measured 437.1975. 5b: ^1H NMR (500 MHz, $CDCl_3$) δ 0.108 and 0.125 (3H and 3H, each s, $2\times SiCH_3$), 0.912 (9H, s, Si-t-Bu), 2.13 (3H, s, OCH_3), 2.15 (1H, dd, J=12.6, 8.3 Hz, 2α-H), 2.31 (1H, d, J=10.8 Hz, 8α-H), 2.33 (1H, 2β-H overlapped with 8α-H), 2.67 and 2.73 (1H and 1H, each m, $=C—CH_2$), 3.25 (1H, ddd, J=10.8, 6.3, 2.8 Hz, 8β, -H), 3.36 (3H, s, $O—CH_3$), 3.55 (2H, m, $CH_2—C\underline{H}_2—O$), 4.61 (2H, s, $O—CH_2—O$), 4.71 (1H, br t, J~7 Hz, 3β-H), 4.94 (1H, d, J=6.3 Hz, 5α-H), 5.64 (1H, dt, J=1.7, 7.1 Hz, =CH); ^{13}C NMR (125 MHz) δ −4.6 ($Si—CH_3$), −4.5 ($Si—CH_3$), 17.9 [$\underline{C}(CH_3)_3$], 21.1 ($CH_3—C=O$), 25.7 [$C(\underline{C}H_3)_3$], 27.8 ($CH_2—C\underline{H}_2—C=$), 38.9 (C_8), 41.2 (C_2), 55.3 ($O—CH_3$), 67.1 ($O—\underline{C}H_2—CH_2$), 67.2 (C_3), 77.1 (C_1), 81.8 (C_5), 96.4 ($O—CH_2—O$), 128.9 ($=\underline{C}—CH_2$), 134.8 (C_4), 169.1 ($CH_3—\underline{C}=O$), 173.0 (C=O); MS (EI) m/z (relative intensity), no M^+, 383 (M^+−OCH_3, 2), 357 (2), 325 (22), 297 (17), 267 (35), 265 (14), 237 (96), 75 (100); HRMS (ESI) exact mass calcd for $C_{20}H_{34}O_7SiNa$ (M^++Na) 437.1972, measured 437.1974.

(f) Reduction of the Acetoxy Lactone 5a (SCHEME II).

[(E)-(1'R,3'R,5'R)-3-[(tert-Butyldimethylsilyl)oxy]-1',5-dihydroxy-4'-[3"-(methoxymethoxy)propylidene]cyclohexyl]methanol (7). (a) To a stirred solution of compound 5a (165 mg, 0.40 mmol) in anhydrous ethanol (5 mL) at 0° C. was added $NaBH_4$ (151 mg, 4.0 mmol) and the mixture was stirred at 0° C. for 1 h, then for 10 h at 6° C., and for 2 h at room temperature. The saturated NH_4Cl was added and the mixture was poured into brine and extracted several times with ether and methylene chloride. The extracts were washed with brine, combined, dried ($MgSO_4$), and evaporated. The oily residue was purified by flash chromatography. Elution with hexane/ethyl acetate (2:8) gave pure triol 7 as a colorless oil (115 mg, 79%). 7: $[\alpha]^{24}_D$−59° (c 1.40 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.087 and 0.110 (3H and 3H, each s, $2\times SiCH_3$), 0.895 (9H, s, Si-t-Bu), 1.66 (1H, dd, J=13.0, 9.1 Hz, 6β-H), 1.69 (1H, dd, J=13.8, 3.1 Hz, 2β-H), 1.84 (1H, s, $O\underline{H}$), 1.96 (1H, ddd, J=13.8, 5.0, 1.7 Hz, 2α-H), 2.04 (1H, ddd, J=13.0, 4.6, 1.7 Hz, 6α-H), 2.54 (1H, s, $O\underline{H}$), 2.63 (2H, m, $=C—CH_2$), 3.34 (3H, s, $O—CH_3$), 3.39 and 3.50 (1H and 1H, after D_2O: each d, J=11.0 Hz, $C\underline{H}_2—OH$), 3.50 (1H, s, $O\underline{H}$), 3.58 (2H, m, $CH_2—C\underline{H}_2—O$), 4.19 (1H, s, $O\underline{H}$), 4.47 (1H, m, w/2=10 Hz, 3β-H), 4.63 (2H, s, $—O—CH_2—O$), 4.89 (1H, m; after D_2O: dd, J=9.1, 4.6 Hz, 5α-H), 5.51 (1H, t, J=8.3 Hz, =CH); 1^3C NMR (125 MHz) δ −5.2 ($Si—CH_3$), −4.7 ($Si—CH_3$), 18.0 [$\underline{C}(CH_3)_3$], 25.7 [$C(\underline{C}H_3)_3$], 27.2 ($CH_2—C\underline{H}_2—C=$), 41.3 (C_2), 44.1 (C_6), 55.4 ($O—CH_3$), 66.4 (C_5), 66.7 ($O—\underline{C}H_2—CH_2$), 70.3 ($CH_2—OH$), 73.7 (C_1), 75.9 (C_3), 96.4 ($O—CH_2—O$), 122.0 ($=\underline{C}—CH_2$), 144.2 (C_4); MS (EI) m/z (relative intensity), no M^+, 358 (M^+−H_2O, 2), 327 (3), 297'(3), 239 (17), 75 (100); HRMS (ESI) exact mass calcd for $C_{18}H_{36}O_6SiNa$ (M^++Na) 399.2179, measured 399.2198.

(b) To a solution of compound 5a (186 mg, 0.45 mmol) in anhydrous THF (17 mL) at 0° C. was added $LiAlH_4$ (128 mg, 3.42 mmol) and the mixture was stirred at 0° C. for 1 h and for 3 h at room temperature. The mixture was carefully poured to the saturated solution of Na_2SO_4 and extracted several times with ethyl acetate and ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The oily residue was purified by flash chromatography. Elution with hexane/ethyl acetate (2:8) gave pure triol 8 as a colorless oil (100 mg, 59%).

(g) Cleavage of the Vicinal Diol 7.

[(E)-(3R,5R)-3-[(tert-Butyldimethylsilyl)oxy]-5-hydroxy-4-[3'-(methoxymethoxy)propylidene]]cyclohexanone (9). Sodium periodate-saturated water (1.2 mL) was added to a solution of the triol 7 (79 mg, 0.21 mmol) in methanol (5 mL) at 0° C. The solution was stirred at 0° C. for 1 h, poured into brine, and extracted with ethyl acetate and ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated. An oily residue was redissolved in hexane/CH_2Cl_2 and applied on a Sep-Pak cartridge. Pure hydroxy ketone 9 (64 mg, 88%) was eluted with hexane/ethyl acetate (7:3) as an oil slowly crystallizing in the refrigerator. 9: $[\alpha]^{24}_{D}$+41° (c 1.45 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.048 and 0.076 (3H and 3H, each s, 2×$SiCH_3$), 0.863 (9H, s, Si-t-Bu), 2.34 (1H, m, one of ═C—CH_2), 2.50 (1H, dd, J=16.0, 6.0 Hz, 2α-H), 2.62 (1H, m, dd, J=16.1, 3.2 Hz, one of 6-H), 2.65 (1H, m, ═C—CH_2), 2.70 (1H, dd, J=16.0, 3.4 Hz, 2β-H), 2.75 (1H, dd, J=16.1, 3.4 Hz, one of 6-H), 3.33 (3H, s, O—CH_3), 3.53 and 3.74 (1H and 1H, each m, CH_2—$C\underline{H}_2$—O), 4.62 (3H, br m, 3β-H and O—CH_2—O), 4.95 (1H, t, J~3.3 Hz, 5α-H), 5.73 (1H, dd, J=10.2, 6.3 Hz, ═CH); ^{13}C NMR (125 MHz) δ −4.9 (Si—CH_3), −4.7 (Si—CH_3), 18.0 [$\underline{C}(CH_3)_3$], 25.6 [$C(\underline{C}H_3)_3$], 28.0 (CH_2—$C\underline{H}_2$—C═), 45.3 (C_2), 48.3 (C_6), 55.4 (O—CH_3), 63.1 (C_5), 65.7 (O—$\underline{C}H_2$—CH_2), 70.3 (C_3), 96.3 (O—CH_2—O), 126.7 (═$\underline{C}$—CH_2), 142.5 (C_4), 208.7 (C_1); MS m/z (relative intensity), no M^+, 313 (M^+−OCH_3, 3), 287 (15), 269 (7), 255 (21), 237 (11), 227 (68), 225 (91), 213 (17), 195 (57), 75 (100); HRMS (ESI) exact mass calcd for $C_{13}H_{21}O_5Si$ (M^+-t-Bu) 287.1315, measured 287.1312.

(h) Protection of 5-Hydroxy Group in the Hydroxy Ketone 9.

[(3R,5R)-3,5-Bis[(tert-Butyldimethylsilyl)oxy]-4-[3'-(methoxymethoxy)propylidene]cyclohexanone (11). To a solution of hydroxy ketone 9 (40 mg, 117 μmol) in anhydrous CH_2Cl_2 (0.4 mL) at −50° C. was added 2,6-lutidine (32 μL, 274 μmol) and t-butyldimethylsilyl triflate (56 μL, 240 μmol). The mixture was stirred for 5 min at −50° C., then it was allowed to warm up to −15° C. and stirred at this temperature for additional 30 min. Benzene and water was added and the mixture was poured into water and extracted with benzene. The extract was washed with saturated $CuSO_4$ and water, dried ($MgSO_4$), and evaporated. The oily residue was redissolved in hexane, and purified by flash chromatography on silica. Elution with hexane/ethyl acetate (95:5) gave pure protected ketone 11 as a colorless oil (30 mg, 57%; 66% based on recovered substrate) and unreacted 9 (6 mg). 11: $[\alpha]^{24}_{D}$−26° (c 0.30 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.019 and 0.065 (3H and 9H, each s, 4×$SiCH_3$), 0.838 and 0.912 (9H and 9H, each s, 2×Si-t-Bu), 2.32 (1H, dd, J=14.1, 10.4 Hz, 2α-H), 2.45 (3H, br m, ═C—CH_2 and 6α-H), 2.53 (1H, ddd, J=14.4, 3.2, 2.1 Hz, 6β-H), 2.75 (1H, ddd, J=14.1, 5.6, 2.1 Hz, 21-H), 3.36 (3H, s, O—CH_3), 3.58 (2H, m, CH_2—$C\underline{H}_2$—O), 4.62 (2H, s, O—CH_2—O), 4.75 (1H, ddd, J=10.4, 5.6, 1.4 Hz, 3β-H), 5.01 (1H, t, J~3.2 Hz, 5α-H), 5.70 (1H, dt, J=1.7, 7.8 Hz, ═CH); ^{13}C NMR (125 MHz) δ −5.08 (Si—CH_3), −5.06 (Si—CH_3), −5.05 (Si—CH_3), −5.00 (Si—CH_3), 17.9 [$\underline{C}(CH_3)_3$], 25.5 [$C(\underline{C}H_3)_3$], 27.7 (CH_2—CH_2—C═), 50.2 (C_6), 52.4 (C_2), 55.2 (O—CH_3), 65.8 (C_3), 67.1 (O—$\underline{C}H_2$—CH_2), 67.8 (C_5), 96.4 (O—CH_2—O), 118.5 (═$\underline{C}$—CH_2), 141.5 (C_4), 207.5 (C_1); MS (EI) m/z (relative intensity) 443 (M^++H, 2), 427 (M^+−CH_3, 5), 401 (55), 371 (15), 339 (20), 75 (100); exact mass calcd for $C_{12}H_{43}O_4Si_2$ (M^+−CH_3) 427.2700, measured 427.2701.

Preparation of the Allylic Esters 13a and 13b.

[(E)- and (Z)-(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]-4'-[3''-(methoxymethoxy)propylidene]cyclohexylidene]acetic Acid Methyl Esters (13a and 13b). To a solution of diisopropylamine (25 μL, 0.18 mmol) in anhydrous THF (0.15 mL) was added n-BuLi (2.5 M in hexanes, 72 μL, 0.18 mmol) under argon at −78° C. with stirring, and methyl(trimethylsilyl)acetate (30 μL, 0.18 mmol) was then added. After 15 min, the ketone 11 (38.4 mg, 84 μmol) in anhydrous THF (0.2 mL) was added. The solution was stirred at −78° C. for additional 2 h and the reaction mixture was quenched with wet ether, poured into brine and extracted with ether and benzene. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. An oily residue was redissolved in hexane and applied on a Sep-Pak cartridge. Pure allylic esters 13a and 13b (37.2 mg, 86%; isomer ratio of 13a:13b=ca. 7:1) were eluted with hexane/ethyl acetate (97:3). Separation of the products was achieved by HPLC (10 mm×25 cm Zorbax-Sil column, 4 mL/min) using the hexane/ethyl acetate (95:5) solvent system. Pure compounds 13a and 13b were eluted at R_V 41 mL and 44 mL, respectively, as colorless oils.

13a: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.006, 0.056, 0.078, 0.107 (each 3H, each s, 4×$SiCH_3$), 0.832 and 0.923 (9H and 9H, each s, 2×Si-t-Bu), 1.87 (1H, t, J=11.8 Hz, 2α-H), 2.28 (1H, br d, J=13.2 Hz, 6α-H), 2.34 (1H, br d, J=13.2 Hz, 6β-H), 2.42 (2H, q, J~7 Hz, ═C—CH_2), 3.36 (3H, s, CH_2—O—$C\underline{H}_3$), 3.55 (2H, m, CH_2—$C\underline{H}_2$—O), 3.70 (3H, s, CO—O—CH_3), 4.14 (1H, dd, J=12.8, 3.8 Hz, 2β-H), 4.45 (1H, br m, 3β-H), 4.62 (2H, s, O—CH_2—O), 4.88 (1H, narr m, 5α-H), 5.55 (1H, br t, J=7.5 Hz, ═C$\underline{H}$—CH_2), 5.65 (1H, br s, ═CH—CO); MS (EI) m/z (relative intensity) no M^+, 499 (M^+−CH_3, 2), 482 (11), 469 (31), 457 (65), 425 (63), 351 (70), 293 (76), 89 (100); HRMS (ESI) exact mass calcd for $C_{26}H_{50}O_6Si_2Na$ 537.3044, measured 537.3018. 13b: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.008, 0.048, 0.057 and 0.063 (each 3H, each s, 4×$SiCH_3$), 0.804 and 0.915 (9H and 9H, each s, 2×Si-t-Bu), 1.95 (1H, br d, J=13.8 Hz, 2β-H), 2.17 (1H, t, J~11.6 Hz, 6β-H), 2.42 (2H, m, ═C—CH_2), 2.55 (1H, ddd, J~12.4, ~5.0, ~1.2 Hz, 6α-H), 3.36 (3H, s, CH_2—O—$C\underline{H}_3$), 3.55 (2H, m, CH_2—$C\underline{H}_2$—O), 3.67 (3H, s, CO—O—CH_3), 3.96 (1H, br d, J=13.8 Hz, 2α-H), 4.51 (1H, br m, 5α-H), 4.62 (2H, s, O—CH_2—O), 4.89 (1H, narr m, 3β-H), 5.50 (1H, br t, J=7.5 Hz, ═C$\underline{H}$—CH_2), 5.80 (1H, br s, ═CH—CO); MS m/z (relative intensity) no M^+, 499 (M^+−CH_3, 4), 482 (14), 469 (34), 457 (82), 425 (69), 351 (58), 293 (59), 89 (100); HRMS (ESI) exact mass calcd for $C_{26}H_{50}O_6Si_2Na$ 537.3044, measured 537.3053.

(j) Reduction of the Allylic Esters 13a and 13b.

2-[(E)- and (Z)-(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]-4'-[3''-(methoxymethoxy)propylidene]cyclohexylidene]ethanol (15a and 15b). Diisobutylaluminum hydride (1.0 M in toluene, 0.35 mL, 0.35 mmol) was slowly added to a stirred solution of the allylic esters 13a and 13b (37.2 mg, 74 μmol) in toluene/methylene chloride (2:1, 1.5 mL) at −78° C. under argon. Stirring was continued at −78° C. for 1 h, the mixture was quenched by addition of potassium sodium tartrate (2 N, 2 mL), aq. HCl (2 N, 2 mL) and H_2O (24 mL), and then diluted with ether and benzene. The organic layer was washed with diluted $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography. Elution with hexane/ethyl acetate (95:5) resulted in partial separation of products: 16 mg of 15a, mixture of 15a and 15b (15 mg) and pure 15b (3 mg; total yield 97%). Rechromatography of the mixed fractions resulted in almost complete separation of the products.

15a (major): ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.007, 0.057, and 0.067 (3H, 6H and 3H, each s, 4×$SiCH_3$), 0.839 and 0.916 (9H and 9H, each s, 2×Si-t-Bu), 1.81 (1H, t, J=11.7 Hz, 2α-H), 2.17 (1H, d, J=13.4Hz, 6α-H), 2.26 (1H, br d, J=13.4Hz, 6β-H), 2.41 (2H, q, J=7 Hz, =C—C$\underline{H}_2$—CH_2), 2.86 (1H, dd, J=12.5, 3.8 Hz, 2β-H), 3.36 (3H, s, O—CH_3), 3.54 (2H, m, CH_2—C$\underline{H}_2$—O), 4.38 (1H, dd, J=10.6, 3.8 Hz, 3β-H), 4.17 (2H, t, J~6 Hz; after D_2O: d, J=6.9 Hz, C$\underline{H}_2$—OH), 4.62 (2H, s, O—CH_2—O), 4.81 (1H, narr m, 5α-H), 5.48 (2H, m, 2×=CH); MS (EI) m/z (relative intensity) 486 (M^+, 3), 468 (30), 454 (17), 441 (32), 429 (24), 423 (34), 89 (100); HRMS (ESI) exact mass calcd for $C_{25}H_{50}O_5Si_2Na$ 509.3095, measured 509.3111.

15b (minor): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.011, 0.054, 0.069 (3H, 3H and 6H, each s, 4×$SiCH_3$), 0.850 and 0.917 (9H and 9H, each s, 2×Si-t-Bu), 1.88 (1H, br d, J=13.4 Hz, 2β-H), 2.03 (1H, t, J=11.4 Hz, 6β-H), 2.42 (2H, m, =C—CH_2), 2.51 (1H, ddd, J=12.0, 4.8, 1.2 Hz, 6α-H), 2.75 (1H, br d, J=13.4 Hz, 2a:-H), 3.36 (3H, s, O—CH_3), 3.55 (2H, m, CH_2—C$\underline{H}_2$—O), 4.02 and 4.15 (1H and 1H, each m; after D_2O: each dd, J=11.8, 7.2 Hz, CH_2—OH), 4.40 (1H, br m, 50: -H), 4.62 (2H, s, O—CH_2—O), 4.90 (1H, narr m, 3β-H), 5.53 (1H, br t, J=7.4 Hz, =C$\underline{H}$—CH_2), 5.71 (1H, t, J=7.2 Hz, =C$\underline{H}$—CH_2—OH); MS (EI) m/z (relative intensity) 486 (M^+, 5), 468 (27), 454 (11), 441 (22), 429 (30), 423 (29), 89 (100); HRMS (ESI) exact mass calc. for $C_{25}H_{50}O_5Si_2Na$ 509.3095, measured 509.3108.

(k) Conversion of the Allylic Alcohols 15a and 15b into Phosphine Oxides 17a and 17b.

[2-[(E)- and (Z)-(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]-4'-[3"-(methoxymethoxy)propylidene]cyclohexylidene]ethyl]diphenylphosphine Oxides (17a and 17b). To the allylic alcohols 15a and 15b (ca. 7:1, 34 mg, 70 μmol) in anhydrous THF (0.8 mL) was added n-BuLi (2.5 M in hexanes, 28 μL, 70 μmol) under argon at 0° C. with stirring. Freshly recrystallized tosyl chloride (14.0 mg, 73 μmol) was dissolved in anhydrous THF (190 μL) and added to the allylic alcohol-BuLi solution. The mixture was stirred at 0° C. for 5 min and set aside at 0° C. In another dry flask with air replaced by argon, n-BuLi (2.5 M in hexanes, 140 μL, 0.35 mmol) was added to Ph_2PH (62 μL, 0.34 mmol) in anhydrous THF (420 μL) at 0° C. with stirring. The red solution was siphoned under argon pressure to the solution of tosylate until the orange color persisted (ca. ¼ of the solution was added). The resulting mixture was stirred an additional 40 min at 0° C., and quenched by addition of H_2O (40 μl). Solvents were evaporated under reduced pressure and the residue was redissolved in methylene chloride (1.0 mL) and stirred with 10% H_2O_2 (0.5 mL) at 0° C. for 1 h. The organic layer was separated, washed with cold aq. sodium sulfite and H_2O, dried ($MgSO_4$), and evaporated. The residue was subjected to flash chromatography. Elution with hexane/ethyl acetate (85:15) gave unchanged allylic alcohols (3.9 mg). Subsequent elution with benzene/ethyl acetate (7:3) resulted in partial separation of products: 27.6 mg of 17a, mixture of 17a and 17b (2 mg) and pure 17b (2 mg; total yield 68%). Analytical samples of both isomers were obtained after HPLC (10 mm×25 cm Zorbax-Sil column, 4 mL/min) purification using hexane/2-propanol (9:1) solvent system. Pure oily compounds 17a and 17b were eluted at R_V 41 mL and 44 mL, respectively.

17a: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.031, −0.013, 0.017, and 0.024 (each 3H, each s, 4×$SiCH_3$), 0.795 and 0.899 (9H and 9H, each s, 2×Si-t-Bu), 1.47 (1H, br t, J~11 Hz, 2α-H), 2.06 (1H, br m, 6α-H), 2.23 (1H, d, J=13.5 Hz, 6β-H), 2.37 (2H, q, J=7.0, =C—C$\underline{H}_2$—CH_2), 2.62 (1H, dd, J=12.8, 4.5 Hz, 2β-H), 3.34 (3H, s, O—CH_3), 3.51 (2H, m, CH_2—C$\underline{H}_2$—O), 4.33 (1H, dd, J=10.6, 4.5 Hz, 3 β-H), 3.15 (2H, dd, J=15.2, 7.6 Hz, CH_2—PO), 4.60 (2H, s, O—CH_2—O), 4.74 (1H, narr m, 5α-H), 5.28 (1H, m, =C$\underline{H}$—CH_2—PO), 5.44 (1H, t, J~7 Hz, =C$\underline{H}$—CH_2—CH_2), 7.45, 7.52 and 7.73 (4H, 2H and 4H, each m, Ar—H); MS (EI) m/z (relative intensity) no M^+, 613 (100), 538 (9), 481 (31), 449 (22); HRMS (ESI) exact mass calcd for $C_{37}H_{59}O_5Si_2PNa$ 693.3536, measured 693.3506.

17b: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.035, 0.018, 0.022, and 0.030 (each 3H, each s, 4×$SiCH_3$), 0.822 and 0.885 (9H and 9H, each s, 2×Si-t-Bu), 1.47 (1H, br d, J=12.9 Hz, 2β-H), 1.93 (1H, m, 6β-H), 2.36 (2H, q, J=7.2 Hz, =C—CH_2), 2.46 (2H, br m, 2α- and 6α-H), 3.03 and 3.17 (1H and 1H, each m, CH_2—PO), 3.35 (3H, s, O—CH_3), 3.50 (2H, m, CH_2—C$\underline{H}_2$—O), 4.36 (1H, dd, J=10.6, 4.0 Hz, 5α-H), 4.60 (2H, s, O—CH_2—O), 4.75 (1H, narr m, 3β-H), 5.39 (1H, m, =C$\underline{H}$—CH_2—PO), 5.44 (1H, br t, J=7.3 Hz, =C$\underline{H}$—CH_2), 7.4-7.75 (1 OH, br m, Ar—H); MS (EI) m/z (relative intensity) no M^+, 613 (100), 538 (28), 481 (90), 449 (80); HRMS (ESI) exact mass calcd for $C_{37}H_{59}O_5Si_2PNa$ 693.3536, measured 693.3538.

(1) Wittig-Horner Coupling of the Protected 25-Hydroxy Grundmann's

1α-[(tert-Butyldimethylsilyl)oxy]-2-[3'-(methoxymethoxy)propylidene]-25-[(triethylsilyl)oxy]-19-norvitamin D_3 tert-Butyldimethylsilyl Ether (20). To a solution of phosphine oxide 17a (15.5 mg, 23 μmol) in anhydrous THF (0.25 mL) at −78° C. was slowly added phenyilithium (1.8 M in cyclohexane/ether, 13 μL, 23 μmol) under argon with stirring. The solution turned deep orange. The mixture was stirred at −78° C. for 20 min and a precooled (−78° C.) solution of protected hydroxy ketone 19a (19 mg, 48 μmol), prepared according to published procedure [Sicinski et al., J. Med. Chem. 37, 3730 (1994)], in anhydrous THF (0.25 mL) was slowly added. The mixture was stirred under argon at −78° C. for 3 h and at 6° C. for 16 h. Ethyl acetate and water were added, and the organic phase was washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in hexane, applied on a silica Sep-Pak cartridge, and washed with hexane/ethyl acetate (98:2, 10 mL) to give 19-norvitamin derivative 20 (9.5 mg, 48%). The Sep-Pak was then washed with hexane/ethyl acetate (96:4, 10 mL) to recover some unchanged C,D-ring ketone 19a (10 mg), and with ethyl acetate (10 mL) to recover diphenylphosphine oxide 17a (1 mg). 20: UV (in hexane) λ_{max} 244.0, 252.5, 262.5 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.015, 0.056, 0.061, and 0.069 (each 3H, each s, 4×$SiCH_3$), 0.556 (3H, s, 18-H_3), 0.565 (6H, q, J=7.9 Hz, 3×$SiCH_2$), 0.821 and 0.921 (9H and 9H, each s, 2×Si-t-Bu), 0.930 (3H, d, J~7 Hz, 21-H_3), 0.947 (9H, t, J=7.9 Hz, 3×$SiCH_2CH_3$), 1.191 (6H, s, 26- and 27-H_3), 1.79 (1H, t, J=12.2 Hz, 10α-H), 1.90 (1H, m), 2.00 (2H, m), 2.20 (1H, br d, J=13.2 Hz, 4β-H), 2.29 (1H, br d, J=13.2 Hz, 4α-H), 2.41 (2H, q, J~7 Hz, =CH—C$\underline{H}_2$) 2.79 (1H, br d, J=12.6 Hz, 9β-H), 3.04 (1H, dd, J=12.4, 4.5 Hz, 10β-H), 3.36 (3H, s, O—CH_3), 3.54 (2H, m, CH_2—C$\underline{H}_2$—O), 4.35 (1H, m, w/2=21 Hz, 1β-H), 4.62 (2H, s, O—CH_2—O), 4.81 (1H, t, J~2.7 Hz, 3α-H), 5.47 (1H, dt, J=1.5, 7.6 Hz, $\underline{H}$C=C—CH_2), 5.87 and 6.12 (1H and 1H, each d, J=11.0 Hz, 7- and 6-H).

(m) Hydrolysis of the Silyl Protecting Groups in the 19-Norvitamin D_3 Derivative 20.

1α,25-Dihydroxy-2-[3'-(methoxymethoxy)propylidene]-19-norvitamin D_3 (21). To a solution of the protected 19-norvitamin D_3 20 (3.0 mg, 3.5 μmol) in anhydrous THF (200 μL) was added tetrabutylammonium fluoride (1.0 M in THF, 210 μL, 210 μmol). The mixture was stirred under argon at room temperature for 18 h, poured into brine and extracted with ethyl acetate. Organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by HPLC (10 mm×25 cm Zorbax-Sil column, 4 mL/min) using hexane/2-propanol (75:25) solvent system. Analytically pure 19-norvitamin 21 (1.27 mg, 71%) was collected at R_V 26 mL. The compound gave also a single peak on reversed-phase HPLC (6.2 mm×25 cm Zorbax-ODS column, 2 mL/min) using methanol/water (8:2) solvent system; it was collected at R_V 35 mL. 21: UV (in EtOH) λ_{max} 243.5, 252.0, 262.0 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 0.549 (3H, s, 18-H_3), 0.940 (3H, d, J=6.4 Hz, 21-H_3), 1.220 (6H, s, 26- and 27-H_3), 2.38 (1H, m, one of ═CH—$C\underline{H}_2$), 2.47 (2H, narr m, 4α- and 4β-H), 2.59 (1H, m, one of ═CH—$C\underline{H}_2$), 2.82 (1H, br d, J=12.8 Hz, 9β-H), 3.14 (1H, dd, J=13.1, 4.9 Hz, 10β-H), 3.34 (3H, s, O—CH_3), 3.55 and 3.63 (1H and 1H, each m, CH_2—$C\underline{H}_2$—O), 4.44 (1H, m, w/2=20 Hz, 1β-H), 4.62 (2H, s, O—CH_2—O), 4.84 (1H, m, w/2=10 Hz, 3α-H), 5.68 (1H, t, J=7.4 Hz, $\underline{H}C$═C—CH_2), 5.88 and 6.31 (1H and 1H, each d, J=11.2 Hz, 7- and 6-H); HRMS (ESI) exact mass calcd for $C_{31}H_{52}O_5Na$ 527.3712, measured 527.3702.

Example II

Preparation of 1α,25-dihydroxy-2-(3'-hydroxypropylidene)-19-norvitamin D_3 compounds

Referring first to SCHEME I the keto lactone 4 was obtained from commercial (−)-quinic acid as described in the Example I (a-c).

(a) Preparation of the Phosphonium Bromide B.

[3-[(tert-Butyldimethylsilyl)oxy]propyl]triphenylphosphonium bromide (B). To a solution of 1-bromo-3-[(tert-butyldimethylsilyl)oxy]propane (2.18 g, 8.56 mmol) in anhydrous benzene (1.6 mL) was added triphenylphoshine (2.64 g, 10.2 mmol) under argon with stirring. The mixture was heated at 85° C. for 18 h and cooled to room temperature. The liquid was decanted and the solid residue was grounded with spatula, filtered and washed several times with ether. Colorless crystals of phosphonium salt B (3.7 g) were purified by silica column chromatography. Pure salt B (3.04 g, 69%) was eluted with chloroform/methanol (96:4). B: ^1H NMR (500 MHz, $CDCl_3$) δ 0.039 (6H, s, 2×$SiCH_3$), 0.857 (9H, s, Si-t-Bu), 1.93 (2H, m, CH_2—$C\underline{H}_2$—CH_2), 3.86-3.94 (4H, br m, CH_2—$C\underline{H}_2$—O and P—CH_2), 7.70, 7.79 and 7.85 (6H, 3H and 6H, each m, Ar—H).

(b) Wittig Reaction of the 4-Ketone 4 with the ylide generated from B.

[(E)- and (Z)-(1R,3R,5R)-1-Acetoxy-3-[(tert-butyldimethylsilyl)oxy]-6-oxa-4-[3'-((tert-butyldimethylsilyl)oxy)propylidene]bicyclo[3.2.1]octan-7-one (6a and 6b). To the phoshonium bromide B (1.55 g, 3.04 mmol) in anhydrous THF (42 mL) at −20° C. was added dropwise n-BuLi (2.0 M in cyclohexane, 1.50 mL, 3.00 mmol) under argon with stirring. and the solution was stirred at −20° C. for 15 min. The orange-red mixture was cooled to −45° C. and siphoned during 15 min to a solution of keto acetate 4 (700 mg, 2.13 mmol) in anhydrous THF (24 mL). The reaction mixture was stirred at −40° C. for 2 h and stopped by addition of brine cont. 1% HCl. Ethyl acetate (30 mL), benzene (20 mL), ether (10 mL), saturated $NaHCO_3$ (10 mL), and water (10 ml) were added and the mixture was vigorously stirred at room temperature for 18 h. Then an organic phase was separated, washed with brine, dried ($MgSO_4$), and evaporated. The residue (consisting mainly with isomeric 6a and 6b in the ratio of ca. 3:2) was purified by flash chromatography on silica. Elution with hexane/ethyl acetate (9:1) gave the mixture of products 6a and 6b (905 mg, 87%). Analytical samples of both isomers were obtained after HPLC (10 mm×25 cm Zorbax-Sil column, 4 mL/min) separation using hexane/ethyl acetate (9:1) solvent system. Pure oily compounds 6a and 6b were eluted at R_V 28 mL and 29 mL, respectively.

6a: ^1H NMR (500 MHz, $CDCl_3$) δ 0.049 and 0.073 (6H and 6H, each s, 4×$SiCH_3$), 0.889 and 0.914 (9H and 9H, each s, 2×Si-t-Bu), 2.01 (1H, br t, J=11.0 Hz, 2α-H), 2.07 (1H, d, J=10.5 Hz, 8α-H), 2.13 (3H, s, OAc), 2.26-2.36 (3H, m, 2β-H overlapped with ═C—CH_2), 3.29 (1H, ddd, J=10.5, 6.4, 2.8 Hz, 8β-H), 3.65 (2 H, m, CH_2—$C\underline{H}_2$—O), 4.40 (1H, ~t, J=8.5 Hz, 3β-H), 5.50 (1H, d, J=6.4 Hz, 5α-H), 5.71 (1H, t, J=7.3 Hz, ═CH), MS (EI) m/z (relative intensity) no M^+, 469 (M^+-Me, 1), 427 (64), 367 (13), 337 (26), 73 (100); HRMS (ESI) exact mass calcd for $C_{24}H_{44}O_6Si_2Na$ (M^++Na) 507.2574, measured 507.2575.

6b: ^1H NMR (500 MHz, $CDCl_3$) δ 0.042 (6H, s, 2×$SiCH_3$), 0.098 and 0.117 (3H and 3H, each s, 2×$SiCH_3$), 0.885 and 0.907 (9H and 9H, each s, 2×Si-t-Bu), 2.13 (3H, s, OAc), 2.14 (1H, m, 2α-H), 2.31 (1H, 2β-H overlapped with 8α-H), 2.32 (1H, d, J=11.0 Hz, 8α-H), 2.51 and 2.64 (1H and 1H, each m, ═C—CH_2), 3.24 (1H, m, 8β-H), 3.62 (2H, m, CH_2—$C\underline{H}_2$—O), 4.69 (1H, ~t, J=7.2 Hz, 3β-H), 4.93 (1H, d, J=6.3 Hz, 5α-H), 5.63 (1H, t, J=7.0 Hz, ═CH), MS (EI) m/z (relative intensity) no M^+, 469 (M^+−Me, 1), 427 (32), 367 (13), 337 (40), 73 (100); HRMS (ESI) exact mass calcd for $C_{24}H_{44}O_6Si_2Na$ (M^++Na) 507.2574, measured 507.2560.

(c) Reduction of the Acetoxy Lactones 6a and 6b (SCHEME II).

[(E)- and (Z)-(1'R,3'R,5'R)-3-[(tert-Butyldimethylsilyl)oxy]-1',5-dihydroxy-4'-[3"-[((tert-butyldimethylsilyl)oxy)propylidene]cyclohexyl]]methanol (8a and 8b). To a stirred solution of compounds 6a and 6b (150 mg, 0.309 mmol) in anhydrous ethanol (4 mL) at 0° C. was added $NaBH_4$ (116 mg, 3.09 mmol) and the mixture was stirred at room temperature for 21 h. The mixture was poured to the saturated NH_4Cl and extracted several times with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The oily residue was purified by silica chromatography. Elution with hexane/ethyl acetate (4:6) gave a semicrystalline mixture oftriols 8a and 8b (136 mg, 98%).

8a (major): $[\alpha]^{24}_D$−53° (c 1.00 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.077, 0.082, 0.084 and 0.110 (4×3H, each s, 4×$SiCH_3$), 0.887 and 0.902 (9H and 9H, 2×s, 2×Si-t-Bu), 1.58 (1H, dd, J=12.8, 10.2 Hz, 6'β-H), 1.62 (1H, dd, J=14.0, 2.8 Hz, 2'β-H), 2.03 (1H, ddd, J=14.0, 3.9, 1.9 Hz, 2'α-H), 2.11 (1H, ddd, J=12.8, 4.5, 1.9 Hz, 6'α-H), 2.46 and 2.66 (1H and 1H, each m, ═C—CH_2), 3.35 and 3.47 (1H and 1H, after D_2O: 2×d, J=10.8 Hz, 1-H_2), 3.68 (2H, m, CH_2—$C\underline{H}_2$—O), 4.46 (1H, ~t, J=3.3 Hz, 3'β-H), 4.88 (1H, after D_2O: dd, J=10.2, 4.5 Hz, 5'α-H), 5.45 (1H, t, J=8.6 Hz, ═CH); ^{13}C NMR (125 MHz) δ −5.6 (Si—CH_3), −5.38 (Si—CH_3), −5.36 (Si—CH_3), −4.5 (Si—CH_3), 17.9 [$\underline{C}(CH_3)_3$], 18.4 [$\underline{C}(CH_3)_3$], 25.7 [$C(\underline{C}H_3)_3$], 26.0 [$C(\underline{C}H_3)_3$], 29.2 (CH_2—$C\underline{H}_2$—C═), 40.4 ($C_{2'}$), 44.1 ($C_{6'}$), 62.2 (O—$\underline{C}H_2$—CH_2), 66.2 ($C_{5'}$), 70.3 (C_1), 73.8 ($C_{1'}$), 74.1 ($C_{3'}$), 121.9 (═$\underline{C}$—CH_2), 145.0 ($C_{4'}$), HRMS (ESI) exact mass calcd for $C_{22}H_{46}O_5Si_2Na$ (M^++Na) 469.2824, measured 469.2781.

(d) Cleavage of the Vicinal Diols 8a and 8b.

[(E)- and (Z)-(3R,5R)-3-[(tert-Butyldimethylsilyl)oxy]-5-hydroxy-4-[3'-[((tert-butyldimethylsilyl)oxy)propylidene]]cyclohexanone (10a and 10b). Sodium periodate-saturated water (1.6 mL) was added to a solution of the triols 8a and 8b (104 mg, 0.233 mmol) in methanol (8 mL) at 0° C. The solution was stirred at 0° C. for 1 h, poured into brine, and extracted with ethyl acetate and ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated. An oily residue was dissolved in hexane/CH_2Cl_2 and applied on a Sep-Pak cartridge. Hydroxy ketones 10a and 10b (85 mg, 88%) were eluted with hexane/ethyl acetate (8:2) as an oil slowly crystallizing in the refrigerator. 10a (major): $[\alpha]^{24}_{D}+55°$ (c 1.17 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.042, 0.065 and 0.074 (3H, 6H and 3H, each s, 4×$SiCH_3$), 0.849 and 0.880 (9H and 9H, each s, 2×Si-t-Bu), 2.28 (1H, m, one of =C—CH_2), 2.50 (1H, dd, J=16.2, 5.4 Hz, 2α-H), 2.55-2.70 (3H, m, 2β-H overlapped with one of 6-H and =C—CH_2), 2.77 (1H, dd, J=16.2, 2.5 Hz, one of 6-H), 3.62 (1H, dt, J=2.6, 10.2 Hz, one of CH_2—$C\underline{H}_2$—O), 3.85 (1H, m, one of CH_2—$C\underline{H}_2$—O), 4.60 (1H, m, 3β-H), 4.90 (1H, narr m, 5α-H), 5.66 (1H, dd, J=10.5, 6.0 Hz, =CH); ^{13}C NMR (125 MHz) δ −5.6 (Si—CH_3), −5.4 (Si—CH_3), −4.9 (Si—CH_3), −4.6 (Si—CH_3), 18.0 [$\underline{C}(CH_3)_3$], 18.5 [$\underline{C}(CH_3)_3$], 25.7 [$C(\underline{C}H_3)_3$], 26.0 [$C(\underline{C}H_3)_3$], 30.7 (CH_2—$C\underline{H}_2$—C=), 45.1 (C_2), 47.9 (C_6), 63.0 (C_5), 61.8 (O—$\underline{C}H_2$—CH_2), 70.8 (C_3), 127.5 (=$\underline{C}$—CH_2), 142.9 (C_4), 208.9 (C_1); MS m/z (relative intensity) no M^+, 399 (M^+−Me, 2), 357 (69), 339 (12), 327 (41), 299 (9), 265 (10), 225 (81), 73 (100); HRMS (ESI) exact mass calcd for $C_{21}H_{42}O_4Si_2Na$ (M^++Na) 437.2519, measured 437.2537.

(e) Protection of 5-Hydroxy Group in the Hydroxy Ketone 10a and 10b.

[(3R,5R)-3,5-Bis[(tert-Butyldimethylsilyl)oxy]-4-[3'-[((tert-butyldimethylsilyl)oxy)propylidene]cyclohexanone (12). To a solution of hydroxy ketones 10a and 10b (22 mg, 53 μmol) in anhydrous CH_2Cl_2 (0.2 mL) at −50° C. was added 2,6-lutidine (14.5 μL, 124 μmol) and t-butyldimethylsilyl triflate (25 μL, 106 μmol). The mixture was stirred at −50° C., for 50 min. Cold and wet CH_2CH_2 was added and the mixture was poured into water and extracted with CH_2CH_2. The extract was washed with saturated $CuSO_4$ and water, dried ($MgSO_4$), and evaporated. The oily residue was redissolved in hexane, and purified by flash chromatography on silica. Elution with hexane/ethyl acetate (95:5) gave pure protected ketone 12 as a colorless oil (18 mg, 64%; 74% based on recovered substrates) and a mixture of unreacted 10a and 10b (3 mg).

12: $[\alpha]^{24}_{D}-17°$ (c 1.35 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.008 (3H, s, $SiCH_3$), 0.061 (15H, s, 5×$SiCH_3$), 0.833, 0.900 and 0.910 (3×9H, each s, 3×Si-t-Bu), 2.32 (1H, dd, J=14.2, 10.4 Hz, 2α-H), 2.32-2.43 (2H, br m, =C—CH_2), 2.43 (1H, dd, J=14.4, 2.8 Hz, 6α-H), 2.52 (1H, ddd, J=14.4, 3.4, 2.2 Hz, 6β-H), 2.75 (1H, ddd, J=14.2, 5.6, 2.2 Hz, 2β-H), 3.65 and 3.71 (each 1H, each m, CH_2—$C\underline{H}_2$—O), 4.76 (1H, ddd, J=10.4, 5.6, 1.7 Hz, 313-H), 5.01 (1H, ~t, J=3.2 Hz, 5α-H), 5.70 (1H, dt, J=1.7, 7.6 Hz, =CH); ^{13}C NMR (125 MHz) δ −5.27 (Si—CH_3), −5.25 (Si—CH_3), −5.01 (Si—CH_3), −5.00 (Si—CH_3), −4.95 (Si—CH_3), −4.89 (Si—CH_3), 17.9 [$\underline{C}(CH_3)_3$], 18.3 [$\underline{C}(CH_3)_3$], 18.4 [$C(\underline{C}H_3)_3$], 25.6 [$C(\underline{C}H_3)_3$], 25.8 [$C(\underline{C}H_3)_3$], 26.0 [$C(CH_3)_3$], 29.7 (CH_2—$C\underline{H}_2$—C=), 50.4 (C_6), 52.5 (C_2), 62.8 (O—$\underline{C}H_2$—CH_2), 65.9 (C_3), 67.9 (C_5), 119.1 (=$\underline{C}$—CH_2), 141.1 (C_4), 207.5 (C_1); MS (EI) m/z (relative intensity) no M^+, 513 (M^+−Me, 2), 471 (74), 381 (5), 339 (63), 73 (100); exact mass calcd for $C_{27}H_{56}O_4Si_3$ (M^+−C_4H_9) 471.2782, measured 471.2796.

(f) Preparation of the Allylic Esters 14a and 14b.

[(E)- and (Z)-(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]-4'-[3"-[((tert-butyldimethylsilyl)oxy)propylidene]cyclohexylidene]acetic Acid Methyl Esters (14a and 14b). To a solution of diisopropylamine (49 μL, 0.363 mmol) in anhydrous THF (0.37 mL) was added n-BuLi (2.5 M in hexanes, 146 μL, 0.365 mmol) under argon at −78° C. with stirring, and methyl(trimethylsilyl)acetate (60.5 μL, 0.366 mmol) was then added. After 15 min, the ketone 12 (76.5 mg, 0.145 μmol) in anhydrous THF (0.45 mL) was added. The solution was stirred at −78° C. for additional 70 min and the reaction mixture was quenched with wet ether, poured into brine and extracted with ether and benzene. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. An oily residue was redissolved in hexane and applied on a Sep-Pak cartridge. Pure allylic esters 14a and 14b (60 mg, 68%; isomer ratio of 14a:14b=ca. 6:1) were eluted with hexane/ethyl acetate (98.5:1.5).

14a (major): $[\alpha]^{24}_{D}$: −33 (c 0.48 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ −0.014, 0.054, 0.059, 0.070, 0.080 and 0.109 (each 3H, each s, 6×$SiCH_3$), 0.830, 0.845 and 0.926 (each 9H, each s, 3×Si-t-Bu), 1.87 (1H, t, J=12 Hz, 2'α-H), 2.26 (1H, br d, J=13.2 Hz, 6'α-H), 2.33 (1H, br d, J=13.2 Hz, 6'β-H), 2.3-2.4 (2H, m, =C—CH_2), 3.6-3.7 (2H, m, CH_2—$C\underline{H}_2$—O), 3.71 (3H, s, $COOCH_3$), 4.15 (1H, ddd, J=12.7, 4.9, 1.5 Hz, 2'β-H), 4.46 (1H, dd, J=10.7, 4.9 Hz, 3'β-H), 4.88 (1H, ~t, J=3 Hz, 5'α-H), 5.54 (1H, dt, J=1.5, 7.3 Hz, =CH), 5.65 (1H, br s, 2-H); ^{13}C NMR (125 MHz) δ −5.26 (Si—CH_3), −5.22 (Si—CH_3), −5.14 (Si—CH_3), −4.92 (Si—CH_3), −4.87 (Si—CH_3), −4.77 (Si—CH_3), 17.95[$\underline{C}(CH_3)_3$], 18.38 [$\underline{C}(CH_3)_3$], 18.41 [$\underline{C}(CH_3)_3$], 25.6 [$C(\underline{C}H_3)_3$], 25.9 [$C(\underline{C}H_3)_3$], 26.0 [$C(\underline{C}H_3)_3$], 30.8 (CH_2—$C\underline{H}_2$—C=), 40.7 ($C_{6'}$), 46.5 ($C_{2'}$), 50.9 ($\underline{C}H_3CO$), 63.1 ($\underline{O}$—CH_2—CH_2), 66.5 ($C_{5'}$), 69.6 ($C_{3'}$), 117.0 (=$\underline{C}$—CH_2), 116.9 (C_2), 142.7 ($C_{4'}$), 156.0 ($C_{1'}$), 166.6 (C_1); minor isomer (Z) selected: 5.50 (1H, dt, J=1.5, 7.3 Hz, =CH), 5.80 (1H, br s, 2-H).

(g) Reduction of the Allylic Esters 14a and 14b.

[(E)- and (Z)-(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]-4'-[3"-[((tert-butyldimethylsilyl)oxy)propylidene]cyclohexylidene]ethanol (16a and 16b). Diisobutylaluminum hydride (1.0 M in hexane, 616 μL, 616 μmol) was slowly added to a stirred solution of the allylic esters 14a and 14b (6:1, 60 mg, 103 μmol) in toluene/methylene chloride (2:1, 2.25 mL) at −78° C. under argon. Stirring was continued at −78° C. for 1 h, the mixture was quenched by addition of potassium sodium tartrate (2 N, 2 mL), aq. HCl (2 N, 2 mL) and H_2O (24 mL), and then diluted with ether and benzene. The organic layer was washed with diluted $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography. Elution with hexane/ethyl acetate (95:5) resulted in 49 mg of mixture of products 16a and 16b, yield 86%). Analytical samples of both isomers were obtained after HPLC (10 mm×25 cm Zorbax-Sil column, 4 mL/min) using hexane/ethyl acetate (9:1) solvent system. Pure oily compounds 16a and 16b were eluted at R_V 28 mL and 29 mL, respectively.

16a (major): ^1H NMR (500 MHz, $CDCl_3$) δ −0.016, 0.055, 0.059, and 0.068 (3H, 6H, 6H and 3H, each s, 6×$SiCH_3$), 0.831, 0.888 and 0.911 (each 9H, each s, 3×Si-t-Bu), 1.80 (1H, t, J=11.8 Hz, 2'α-H), 2.16 (1H, br d, J=13.2 Hz, 6'α-H), 2.26 (1H, br d, J=13.2 Hz, 6'β-H), 2.34 (2H, m, =C—$C\underline{H}_2$—CH_2), 2.86 (1H, ddd, J=12.4, 4.4, 1.5 Hz, 2'β-H), 3.62 (2H, m, CH_2—$C\underline{H}_2$—O), 4.19 (2H, t, J~6 Hz; after D_2O:d, J=7.0 Hz, 1-H), 4.37 (1H, after D_2O: dm, J=10.4 Hz, 3'β-H), 4.80 (1H, ~t, J=3 Hz, 5'α-H), 5.47 (2H, m, 2×=$C\underline{H}$); ^{13}C NMR (125 MHz) δ −5.28 (2×Si—CH_3), −5.06 (Si—CH_3), −5.00 (Si—CH_3), −4.85 (Si—CH_3), −4.79 (Si—CH_3), 18.0 [$\underline{C}(CH_3)_3$], 18.4 [2×$\underline{C}(CH_3)_3$], 25.6 [$C(\underline{C}H_3)_3$], 25.9 [$C(\underline{C}H_3)_3$], 26.0 [$C(\underline{C}H_3)_3$], 30.8 (CH_2—$C\underline{H}_2$—C=), 40.0 ($C_{2'}$), 45.5 ($C_{6'}$), 58.7 (C_1), 63.2 (O—$\underline{C}H_2$—CH_2), 66.5 ($C_{5'}$), 70.0 ($C_{3'}$), 116.6 (=$\underline{C}$—CH_2), 125.4 (C_2), 137.2 ($C_{1'}$), 143.4 ($C_{4'}$); MS (EI) m/z (relative intensity) no M^+, 538 (M^+-H_2O, 9), 499 (12), 471 (7), 424 (39), 407 (11), 349 (23), 73 (100), HRMS (ESI) exact mass calcd for $C_{29}H_{60}O_4Si_3Na$ (M^++Na) 579.3697, measured 579.3704.

16b (minor): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.029, 0.055, 0.060, 0.064 and 0.069 (3H, 6H, 3H, 3H and 3H, each s, 6×$SiCH_3$), 0.849, 0.898 and 0.918 (each 9H, each s, 3×Si-t-Bu), 1.87 (1H, br d, J=13.8 Hz, 2'β-H), 2.03 (1H, br t, J=11.5 Hz, 6'β-H), 2.34 (2H, m, ═C—CH_2), 2.51 (1H, ddd, J=12.0, 5.0, 1.6 Hz, 6'α-H), 2.76 (1H, br d, J=13.8 Hz, 2'α-H), 3.64 (2H, m, CH_2—$C\underline{H}_2$—O), 4.02 and 4.13 (1H and 1H, each m; after D_2O: each dd, J=11.8, 7.2 Hz, $C\underline{H}_2$—OH), 4.39 (1H, dm, J~10.6 Hz, 5'α-H), 4.89 (1H, br s, 3β-H), 5.52 (1H, dt, J=1.3, 7.5 Hz, ═$C\underline{H}$—CH_2), 5.71 (1H, t, J=7.2 Hz, ═$C\underline{H}$—CH_2—OH); MS (EI) m/z (relative intensity) no M^+, 538 (M^+-H_2O, 4), 499 (6), 471 (4), 424 (12), 407 (6), 349 (11), 73 (100); HRMS (ESI) exact mass calcd for $C_{29}H_{60}O_4Si_3$ (M^+-H_2O) 538.3694, measured 538.3689.

(h) Conversion of the Allylic Alcohols 16a and 16b into Phosphine Oxides 18a and 18b.

[2-[(E)- and (Z)-(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]-4'-[3"-[((tert-butyldimethylsilyl)oxy)propylidene] cyclohexylidene]ethyl]-diphenylphosphine Oxides (18a and 18b). To the allylic alcohols 16a and 16b (5.5:1, 40.5 mg, 70.2 μmol) in anhydrous THF (0.8 mL) was added n-BuLi (2.5 M in hexanes, 35 μL, 87.5 μmol) under argon at 0° C. with stirring. Freshly recrystallized tosyl chloride (14.0 mg, 73 μmol) was dissolved in anhydrous THF (190 μL) and added to the allylic alcohol-BuLi solution. The mixture was stirred at 0° C. for 5 min and set aside at 0° C. In another dry flask with air replaced by argon, n-BuLi (2.5 M in hexanes, 140 μL, 0.35 mmol) was added to Ph_2PH (62 μL, 0.34 mmol) in anhydrous THF (420 μL) at 0° C. with stirring. The red solution was siphoned under argon pressure to the solution of tosylate until the orange color persisted (ca. ¼ of the solution was added). The resulting mixture was stirred an additional 40 min at 0° C., and quenched by addition of H_2O (40 μl). Solvents were evaporated under reduced pressure and the residue was dissolved in methylene chloride (1.0 mL) and stirred with 10% H_2O_2 (0.5 mL) at 0° C. for 1 h. The organic layer was separated, washed with cold aq. sodium sulfite and H_2O, dried ($MgSO_4$), and evaporated. The residue was subjected to flash chromatography. Elution with hexane/ethyl acetate (95:5) gave unchanged allylic alcohols (16.3 mg). Subsequent elution with hexane/ethyl acetate (7:3) resulted in mixture of products: 18a and 18b (25 mg, 49%; 81% based on recovered substrates 16a,b).

18a (major isomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.044, −0.022, 0.011, 0.020, 0.030, and 0.035 (each 3H, each s, 6×$SiCH_3$), 0.787, 0.878 and 0.894 (each 9H, each s, 3×Si-t-Bu), 1.47 (1H, br t, J~11 Hz, 2'ac-H), 2.04 (1H, m, 6'α-H), 2.22 (1H, d, J=13.7 Hz, 6'β-H), 2.28 (2H, m, ═C—$C\underline{H}_2$—CH_2), 2.62 (1H, dd, J=12.8, 4.2 Hz, 2'β-H), 3.58 (2H, m, CH_2—$C\underline{H}_2$—O), 4.32 (1H, dm, J~10 Hz, 3'-H), 3.17 (2H, dd, J=15.2, 7.6 Hz, CH_2—PO), 4.73 (1H, br s, 5'α-H), 5.27 (1H, m, ═$C\underline{H}$—CH_2—CH_2), 5.43 (1H, br t, J~7 Hz, ═$C\underline{H}$—CH_2—PO), 7.46, 7.51 and 7.72 (4H, 2H and 4H, each m, Ar—H); HRMS (ESI) exact mass calcd for $C_{41}H_{69}O_4Si_3PNa$ (M^++Na) 763.4139, measured 763.4157.

Wittig-Horner Coupling of Protected 25-Hydroxy Grundmann's Ketone 19a with the Phosphine Oxides 18a and 18b (SCHEME III).

1α-[(tert-Butyldimethylsilyl)oxy]-2-[3'-[((tert-butyldimethylsilyl)oxy)propylidene]-25-[(triethylsilyl)oxy]-19-norvitamin D_3 tert-Butyldimethylsilyl Ethers (22a and 22b). To a solution of phosphine oxides 18a and 18b (6:1, 20.3 mg, 27.6 μmol) in anhydrous THF (0.3 mL) at −78° C. was slowly added phenyllithium (1.56 M in cyclohexane, 19 μL, 30 μmol) under argon with stirring. The solution turned deep orange. The mixture was stirred at −78° C. for 20 min and a precooled (−78° C.) solution of protected hydroxy ketone 19a (15.4 mg, 39 μmol), prepared according to published procedure [Sicinski et al., J. Med. Chem. 37, 3730 (1994)], in anhydrous THF (80 μL) was slowly added. The mixture was stirred under argon at −78° C. for 3 h and at 6° C. for 19 h. Ethyl acetate, benzene and water were added, and the organic phase was washed with brine, dried ($MgSO_4$), and evaporated. The residue was redissolved in hexane and applied on a silica column. Elution with hexane/ethyl acetate (99.5:0.5) yielded 19-norvitamin derivatives 22a and 22b (8.6 mg, 47% based on recovered substrates). The column was then washed with hexane/ethyl acetate (96:4) to recover some unchanged C,D-ring ketone 19a (7 mg), and with ethyl acetate to recover unreacted diphenylphosphine oxide (5.5 mg). Analytical sample of the main product 22a was obtained by HPLC (10 mm×25 cm Zorbax-Sil column, 4 mL/min) purification using hexane/ethyl acetate (99.8:0.2) solvent system. Pure compound 22a was eluted at R_V 28 mL as a colorless oil. 22a: UV (in EtOH) λ_{max} 244.0, 252.5, 262.5 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.023, 0.052, 0.056, 0.061, 0.063, and 0.070 (each 3H, each s, 6×$SiCH_3$), 0.555 (3H, s, 18-H_3), 0.565 (6H, q, J=7.9 Hz, 3×$SiCH_2$), 0.819, 0.897, and 0.923 (9H and 9H, each s, 3×Si-t-Bu), 0.878 (3H, d, J=7.1 Hz, 21-H_3), 0.947 (9H, t, J=7.9 Hz, 3×$SiCH_2C\underline{H}_3$), 1.190 and 1.191 (3H and 3H, each s, 26- and 27-H_3), 1.79 (1H, t, J=11.6 Hz, 10α-H), 1.90 (1H, m), 2.00 (2H, m), 2.19 (1H, br d, J~14 Hz, 4β-H), 2.27 (1H, br d, J~14 Hz, 4α-H), 2.33 (2H, m, ═CH—$C\underline{H}_2$), 2.79 (1H, br d, J~13 Hz, 9β-H), 3.05 (1H, dd, J=12.0, 4.0 Hz, 10β-H), 3.62 (2H, m, CH_2—$C\underline{H}_2$—O), 4.34 (1H, m, w/2=20 Hz, 1β-H), 4.81 (1H, t, J~2.8 Hz, 3α-H), 5.47 (1H, dt, J~1.5, ~7.5 Hz, $\underline{H}C$═C—CH_2), 5.88 and 6.12 (1H and 1H, each d, J=11.0 Hz, 7- and 6-H); HRMS (ESI) exact mass calcd for $C_{53}H_{104}O_4Si_4Na$ (M^++Na) 939.6909, measured 939.6900.

(j) (20S)-1α-[(tert-Butyldimethylsilyl)oxy]-2-[3'-[((tert-butyldimethylsilyl)oxy)propylidene]-25-[(triethylsilyl)oxy]-19-norvitamin D_3 tert-Butyldimethylsilyl Ethers (23a and 23b).

Protected 19-norvitamin D_3 compounds 23a and 23b were obtained by Wittig-Horner coupling of protected 25-hydroxy Grundmann's ketone 19b with the phosphine oxides 18a and 18b performed analogously to the process described above for the preparation of (20R)-isomers 22a and 22b. The protected vitamins were purified on a silica column, using hexane/ethyl acetate (99.5:0.5) solvent system, and they were obtained in ca. 47% yield. Analytical sample of the protected vitamin 23a was obtained by HPLC (10 mm×25 cm Zorbax-Sil column, 4 mL/min) purification using hexane/ethyl acetate (99.7:0.3) solvent system. Pure compound 23a was eluted at R_V 25 mL as a colorless oil. 23a: UV (in EtOH) λ_{max} 243.5, 252.5, 262.5 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.024, 0.057, 0.059, and 0.069 (3H, 3H, 6H, and 6H, each s, 6×$SiCH_3$), 0.550 (3H, s, 18-H_3), 0.560 (6H, q, J=7.5 Hz, 3×$SiCH_2$), 0.818, 0.895, and 0.923 (each 9H, each s, 3×Si-t-Bu), 0.867 (3H, d, J=7.0 Hz, 21-H_3), 0.943 (9H, t, J=7.5 Hz, 3×$SiCH_2C\underline{H}_3$), 1.191 (6H, s, 26- and 27-H_3), 1.79 (1H, t, J~12 Hz, 10α-H), 1.90 (1H, m), 2.00 (2H, m), 2.19 (1H, br d, J~13 Hz, 4β-H), 2.27 (1H, br d, J~13 Hz, 4α-H), 2.33 (2H, m, ═CH—$C\underline{H}_2$), 2.79 (1H, br d, J~11.5 Hz, 9β-H), 3.05 (1H, dm, J~12 Hz, 101-H), 3.62 (2H, m, CH_2—$C\underline{H}_2$—O), 4.34 (1H, m, w/2=20 Hz, 1β-H), 4.80 (1H, br s, 3α-H), 5.47 (1H, t, J=7.0 Hz, $\underline{H}C$═C—CH_2), 5.88 and 6.11 (1H and 1H, each d, J=11.2 Hz, 7- and 6-H); HRMS

(ESI) exact mass calcd for $C_{53}H_{104}O_4Si_4Na$ (M^++Na) 939.6909, measured 939.6907.

(k) Hydrolysis of the Silyl Protecting Groups in the 19-Norvitamin D_3 Derivatives 22a and 22b.

1α,25-Dihydroxy-2-[3'-hydroxypropylidene]-19-norvitamin D_3 (24a and 24b). To a solution of the protected vitamins 22a and 22b (5.7 mg, 6.2 μmol) in anhydrous THF (4.3 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 372 μL, 372 μmol). The mixture was stirred under argon at room temperature for 18 h, poured into brine and extracted with ethyl acetate and diethyl ether. Organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by HPLC (10 mm×25 cm Zorbax-Sil column, 4 mL/min) using hexane/2-propanol (8:2) solvent system. Pure mixture of 19-norvitamin 24a and 24b was collected at R_V 37.5 mL. Separation of both isomers was easily achieved by reversed-phase HPLC (6.2 mm×25 cm Zorbax-ODS column, 2 mL/min) using methanol/water (8:2) solvent system. Analytically pure E-isomer 24a (2.8 mg, 97%) was collected at R_V 23 mL and Z-isomer 24b (11 μg) at R_V 29 mL.

24a: UV (in EtOH) λ_{max} 243.0, 251.0, 261.5 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 0.549 (3H, s, 18-H_3), 0.940 (3H, d, J=6.3 Hz, 21-H_3), 1.22 (6H, s, 26- and 27-H_3), 2.33 and 2.55 (1H and 1H, each m, $=CH—C\underline{H}_2$), 2.47 (2H, narr m, 4α- and 4β-H), 2.82 (1H, br d, J~13 Hz, 9β-H), 3.16 (1H, dd, J=13.0, 4.8 Hz, 10β-H), 3.66 and 3.76 (1H and 1H, each m, $CH_2—C\underline{H}_2—O$), 4.45 (1H, m, w/2=20 Hz, 1β-H), 4.85 (1H, narr m, 3α-H), 5.66 (1H, t, J=7.3 Hz, $\underline{H}C═C—CH_2$), 5.88 and 6.31 (1H and 1H, each d, J=11.2 Hz, 7- and 6-H); HRMS (ESI) exact mass calcd for $C_{29}H_{48}O_4Na$ (M^++Na) 483.3450, measured 483.3461.

24b:UV (in EtOH) λ_{max} 243.0, 251.5, 262.0 nm; ^1H NMR (800 MHz, $CDCl_3$) δ 0.553 (3H, s, 18-H_3), 0.939 (3H, d, J=6.6 Hz, 21-H_3), 1.22 (6H, s, 26- and 27-H_3), 2.19 (1H, t, J=11.0 Hz, 4β-H), 2.25 (1H, br d, J=14.6 Hz, 10β-H), 2.40 and 2.56 (1H and 1H, each m, $=CH—C\underline{H}_2$), 2.74 (1H, dd, J=13.0, 4.8 Hz, 4α-H), 2.81 (1H, br d, J=12.5 Hz, 9β-H), 2.93 (1H, dd, J=14.6, 3.8 Hz, 10α-H), 3.67 and 3.76 (1H and 1H, each m, $CH_2—C\underline{H}_2—O$), 4.48 (1H, m, w/2=19 Hz, 3α-H), 4.89 (1H, narr m, 1β-H), 5.65 (1H, t, J=8.1 Hz, $\underline{H}C═C—CH_2$), 5.85 and 6.40 (1H and 1H, each d, J=11.0 Hz, 7- and 6-H).

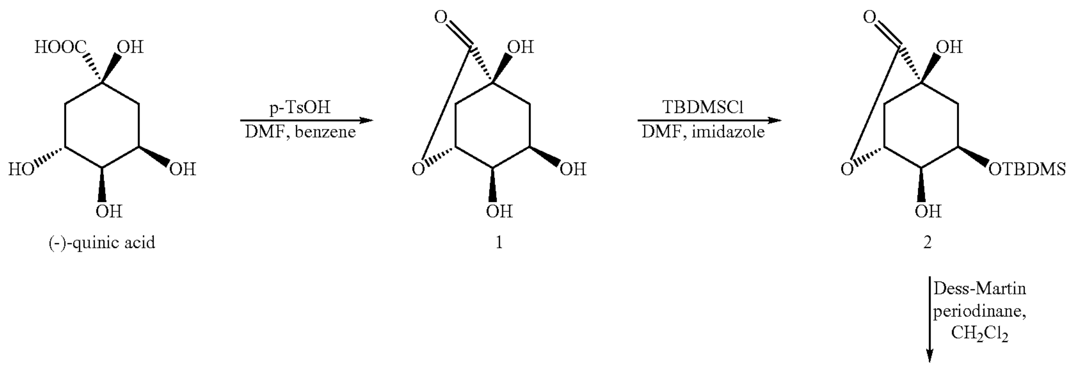
(l) Hydrolysis of the Silyl Protecting Groups in the 19-Norvitamin D_3 Derivatives 22a and 22b.

(20S)-1α,25-Dihydroxy-2-[3'-hydroxypropylidene]-19-norvitamin D_3 (24a and 24b). Vitamins 25a and 25b were obtained by hydrolysis of the silyl protecting groups in the 19-norvitamin derivatives 23a and 23b performed analogously to the process described above for the preparation of (20R)-isomers 24a and 24b. The residue was purified by HPLC (10 mm×25 cm Zorbax-Sil column, 4 mL/min) using hexane/2-propanol (8:2) solvent system. Pure mixture of 19-norvitamin 25a and 25b (95% yield) was collected at R_V 36.5 mL. Separation of both isomers was easily achieved by reversed-phase HPLC (6.2 mm×25 cm Zorbax-ODS column, 2 mL/min) using methanol/water (8:2) solvent system. Analytically pure E-isomer 25a was collected at R_V 18 mL and Z-isomer 25b at R_V 28 mL (ratio of 25a:25b=160:1).

25a: UV (in EtOH) λ_{max} 243.0, 251.5, 261.0 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 0.548 (3H, s, 18-H_3), 0.858 (3H, d, J=6.4 Hz, 21-H_3), 1.21 (6H, s, 26- and 27-H_3), 2.35 and 2.54 (1H and 1H, each m, $=CH—C\underline{H}_2$), 2.47 (2H, narr m, 4α- and 4β-H), 2.82 (1H, br d, J=12.7 Hz, 9β-H), 3.16 (1H, dd, J=13.1, 4.9 Hz, 10β-H), 3.65 and 3.76 (1H and 1H, each m, $CH_2—C\underline{H}_2—O$), 4.45 (1H, m, w/2=25 Hz, 1β-H), 4.85 (1H, narr m, 3α-H), 5.66 (1H, t, J=7.4 Hz, $\underline{H}C═C—CH_2$), 5.88 and 6.31 (1H and 1H, each d, J=11.4 Hz, 7- and 6-H); HRMS (ESI) exact mass calcd for $C_{29}H_{48}O_4Na$ (M^++Na) 483.3450, measured 483.3427.

25b: UV (in EtOH) λ_{max} 243.0, 251.5, 262.0 nm; ^1H NMR (800 MHz, $CDCl_3$) δ 0.550 (3H, s, 18-H_3), 0.854 (3H, d, J=6.6 Hz, 21-H_3), 1.21 (6H, s, 26- and 27-H_3), 2.19 (1H, t, J~12 Hz, 41-H), 2.24 (1H, br d, J=14.6 Hz, 10β-H), 2.40 and 2.56 (1H and 1H, each m, $=CH—C\underline{H}_2$), 2.74 (1H, dd, J=13.2, 4.4 Hz, 4α-H), 2.82 (1H, br d, J=12.4 Hz, 9β-H), 2.92 (1H, dd, J=14.6, 3.7 Hz, 10α-H), 3.61 and 3.72 (1H and 1H, each m, $CH_2—C\underline{H}_2—O$), 4.47 (1H, m, w/2=18 Hz, 3α-H), 4.88 (1H, narr m, 1β-H), 5.65 (1H, t, J~7.5 Hz, $\underline{H}C═C—CH_2$), 5.85 and 6.40 (1H and 1H, each d, J=11.0 Hz, 7- and 6-H).

SCHEME I



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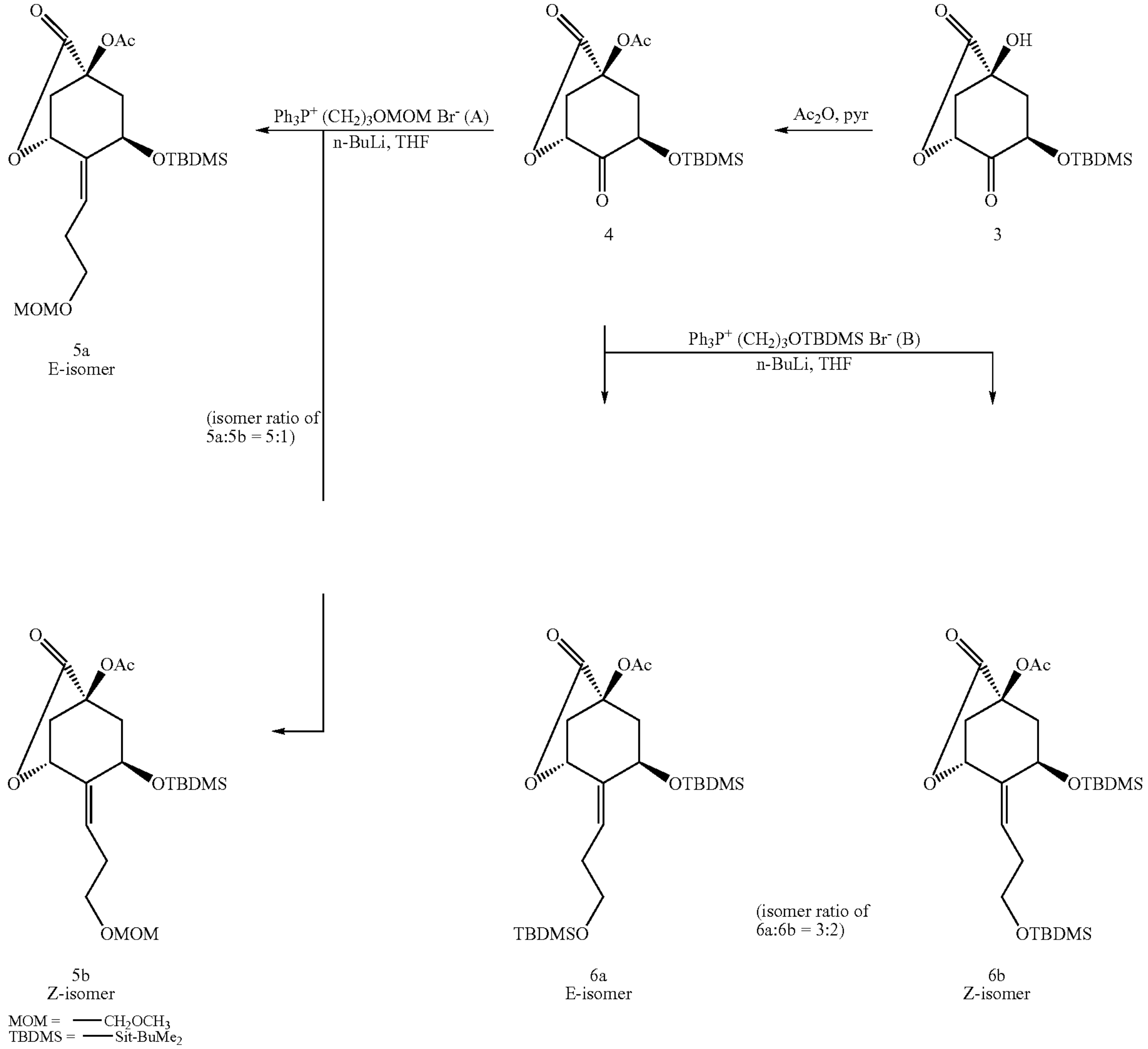

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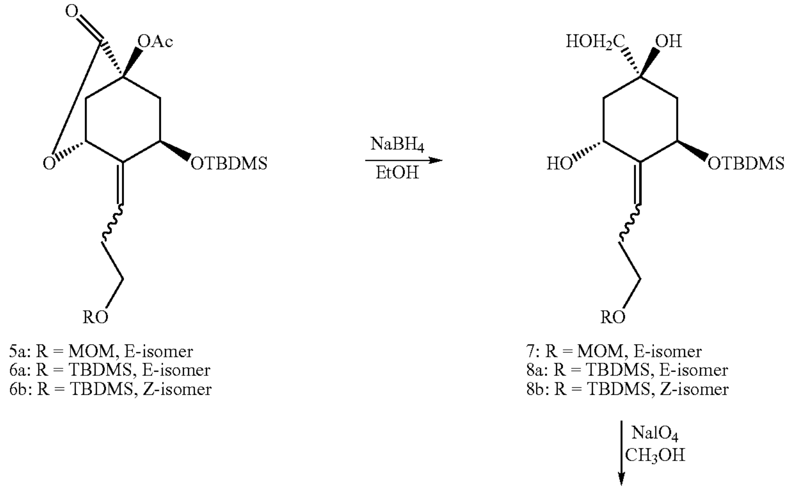

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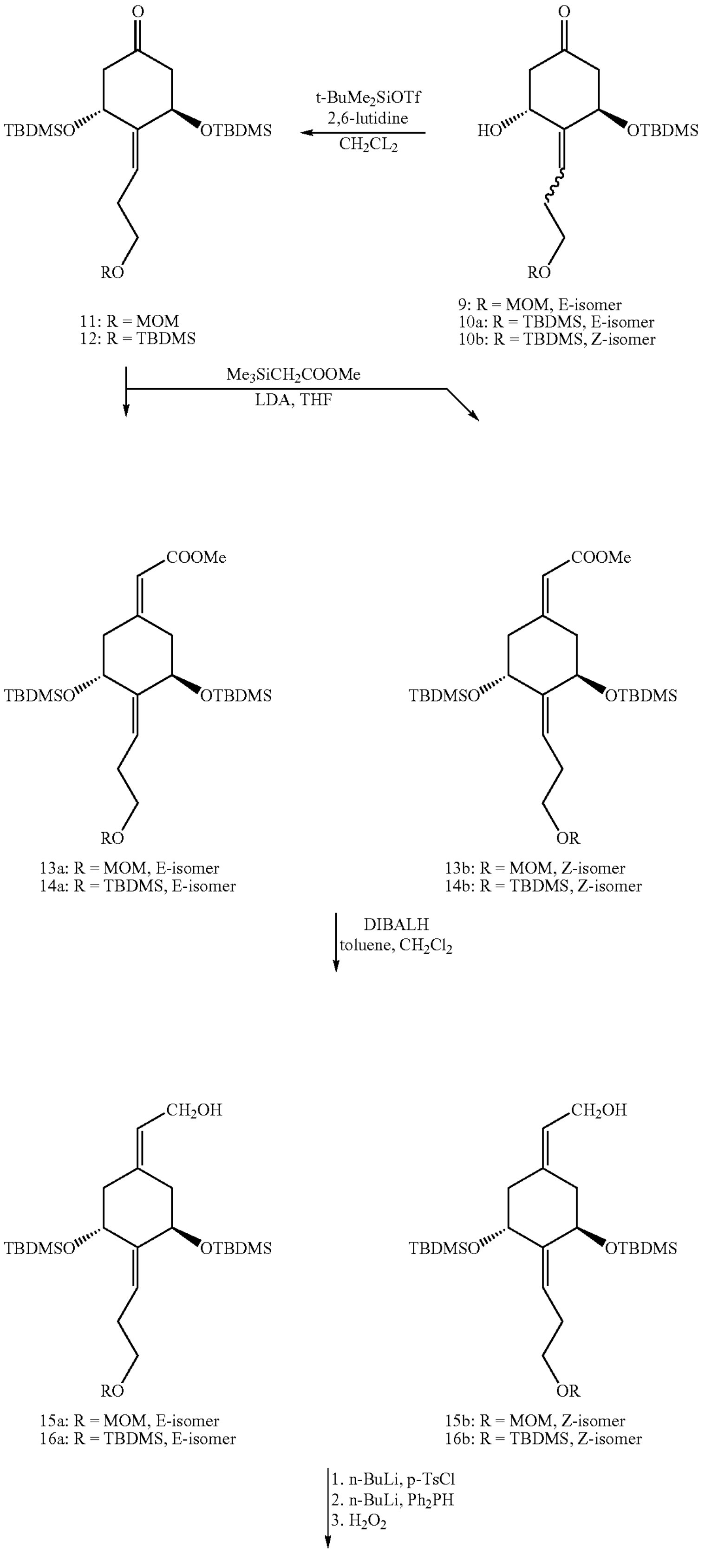

11: R = MOM
12: R = TBDMS

9: R = MOM, E-isomer
10a: R = TBDMS, E-isomer
10b: R = TBDMS, Z-isomer

13a: R = MOM, E-isomer
14a: R = TBDMS, E-isomer

13b: R = MOM, Z-isomer
14b: R = TBDMS, Z-isomer

15a: R = MOM, E-isomer
16a: R = TBDMS, E-isomer

15b: R = MOM, Z-isomer
16b: R = TBDMS, Z-isomer

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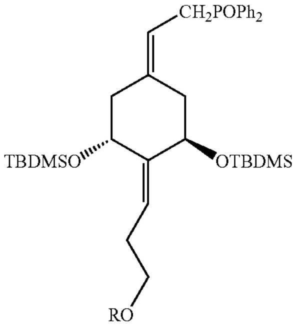
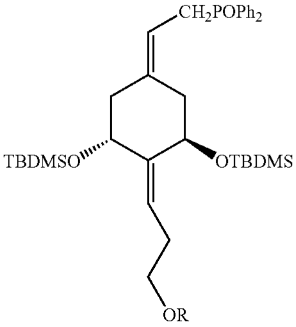
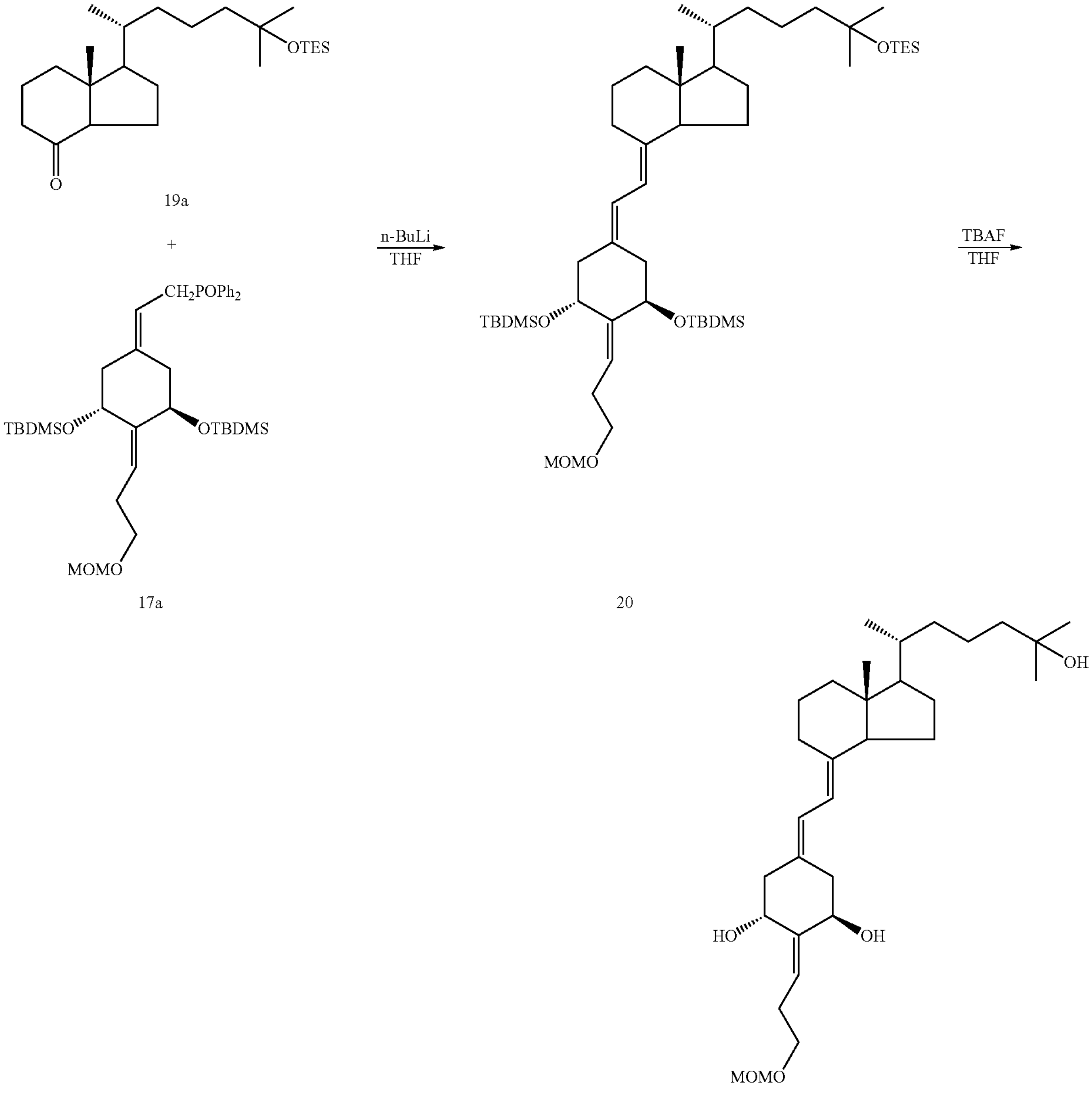

17a: R = MOM, E-isomer
18a: R = TBDMS, E-isomer


17b: R = MOM, Z-isomer
18b: R = TBDMS, Z-isomer

SCHEME III



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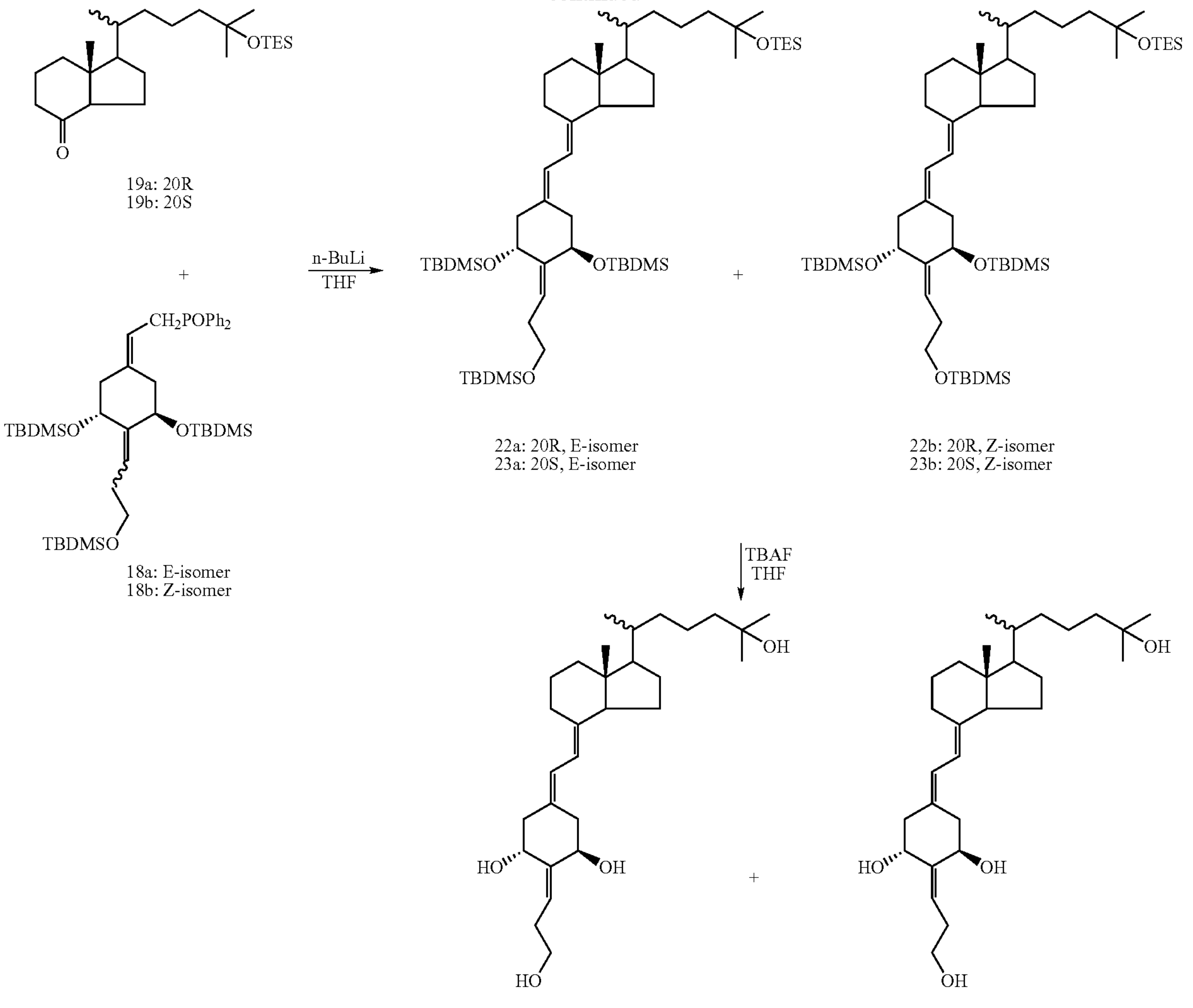


19a: 20R
19b: 20S

18a: E-isomer
18b: Z-isomer

22a: 20R, E-isomer
23a: 20S, E-isomer

22b: 20R, Z-isomer
23b: 20S, Z-isomer

24a: 20R, E-isomer
25a: 20S, E-isomer

24b: 20R, Z-isomer
25b: 20S, Z-isomer

For treatment purposes, the novel compounds of this invention defined by formula I may be formulated for pharmaceutical applications as a solution in innocuous solvents, or as an emulsion, suspension or dispersion in suitable solvents or carriers, or as pills, tablets or capsules, together with solid carriers, according to conventional methods known in the art. Any such formulations may also contain other pharmaceutically-acceptable and non-toxic excipients such as stabilizers, anti-oxidants, binders, coloring agents or emulsifying or taste-modifying agents.

The compounds may be administered orally, topically, parenterally or transdermally. The compounds are advantageously administered by injection or by intravenous infusion or suitable sterile solutions, or in the form of liquid or solid doses via the alimentary canal, or in the form of creams, ointments, patches, or similar vehicles suitable for transdermal applications. Doses of from 0.01 μg to 100 μg per day of the compounds, preferably from about 0.1 μg/day to about 50 μg/day, are appropriate for treatment purposes, such doses being adjusted according to the disease to be treated, its severity and the response of the subject as is well understood in the art. Since the new compounds exhibit specificity of action, each may be suitably administered alone, or together with graded doses of another active vitamin D compound—e.g. 1α-hydroxyvitamin D_2 or D_3, or 1α,25-dihydroxyvitamin D_3—in situations where different degrees of bone mineral mobilization and calcium transport stimulation is found to be advantageous.

Compositions for use in the above-mentioned treatment of psoriasis and other malignancies comprise an effective amount of one or more 2-propylidene-19-nor-vitamin D compound as defined by the above formula I as the active ingredient, and a suitable carrier. An effective amount of such compounds for use in accordance with this invention is from about 0.01 g to about 100 μg per gm of composition, preferably from about 0.1 μg/gm to about 50 μg/gm of the composition, and may be administered topically, transdermally, orally or parenterally in dosages of from about 0.01 μg/day to about 100 μg/day, preferably from about 0.1 μg/day to about 50 μg/day.

The compounds may be formulated as creams, lotions, ointments, topical patches, pills, capsules or tablets, or in liquid form as solutions, emulsions, dispersions, or suspensions in pharmaceutically innocuous and acceptable solvent or oils, and such preparations may contain in addition other pharmaceutically innocuous or beneficial components, such as stabilizers, antioxidants, emulsifiers, coloring agents, binders or taste-modifying agents.

The compounds are advantageously administered in amounts sufficient to effect the differentiation of promyelocytes to normal macrophages. Dosages as described above are suitable, it being understood that the amounts given are to be adjusted in accordance with the severity of the disease, and the condition and response of the subject as is well understood in the art.

The formulations of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops; or as sprays.

For asthma treatment, inhalation of powder, self-propelling or spray formulations, dispensed with a spray can, a nebulizer or an atomizer can be used. The formulations, when dispensed, preferably have a particle size in the range of 10 to 100μ.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient as a physically and chemically stable unit dose comprising either the active ingredient as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

2-Propylidene-19-nor Slow Release Compounds

Modified vitamin D compounds that exhibit a desirable and highly advantageous pattern of biological activity in vivo, namely, the more gradual onset and more prolonged duration of activity, may also be used herein.

Structurally, the key feature of the modified vitamin D compounds having these desirable biological attributes is that they are derivatives of 2-propylidene-19-nor-vitamin D analogs, in which a hydrolyzable group is attached to the hydroxy group at carbon 25 and, optionally, to any other of the hydroxy groups present in the molecule. Depending on various structural factors—e.g. the type, size, structural complexity—of the attached group, these derivatives hydrolyze to the active 2-propylidene-19-nor-vitamin D analog, at different rates in vivo, thus providing for the "slow release" of the biologically active vitamin D compound in the body.

The "slow release" in vivo activity profiles of such compounds can, of course, be further modulated by the use of mixtures of derivatives or the use of mixtures consisting of one or more vitamin D derivative together with underivatized vitamin D compounds.

It is important to stress that the critical structural feature of the vitamin derivatives identified above is the presence of a hydrolyzable group attached to the hydroxy group at carbon 25 of the molecule. The presence of a hydrolyzable group at that position imparts on the resulting derivatives the desirable "slow-release" biological activity profile mentioned above. Other hydroxy functions occurring in the molecule (e.g. hydroxy functions at carbons 1 or 3) may be present as free hydroxy groups, or one or more of them may also be derivatised with a hydrolyzable group.

The "hydrolyzable group" present in the above-mentioned derivatives is preferably an acyl group, i.e. a group of the type Q^1CO—, where Q^1 represents hydrogen or a hydrocarbon radical of from 1 to 18 carbons that may be straight chain, cyclic, branched, saturated or unsaturated. Thus, for example, the hydrocarbon radical may be a straight chain or branched alkyl group, or a straight chain or branched alkenoyl group with one or more double bonds, or it may be an optionally substituted cycloalkyl or cycloalkenyl group, or an aromatic group, such as substituted or unsubstituted phenyl, benzyl or naphthyl. Especially preferred acyl groups are alkanoyl or alkenoyl groups, of which some typical examples are formyl, acetyl, propanoyl, hexanoyl, isobutyryl, 2-butenoyl, palmitoyl or oleoyl. Another suitable type of hydrolyzable group is the hydrocarbyloxycarbonyl group, i.e. a group of the type Q^2—O—CO—, where Q^2 is a C_1 to C_{18} hydrocarbon radical as defined above. Exemplary of such hydrocarbon radicals are methyl, ethyl, propyl, and higher straight chain or branched alkyl and alkenoyl radicals, as well as aromatic hydrocarbon radicals such as phenyl or benzoyl.

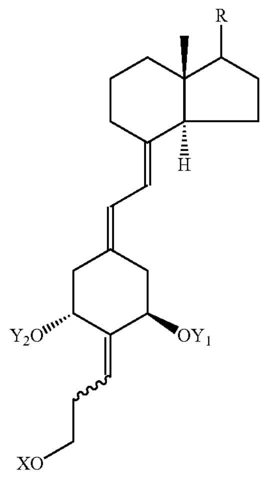
These modified vitamin D compounds are hydrolyzable in vivo to the active analog over a period of time following administration, and as a consequence regulate the in vivo availability of the active analog, thereby also modulating their activity profile in vivo. The term "activity profile" refers to the biological response over time of vitamin D compounds. Individual modified compounds, or mixtures of such compounds, can be administered to "fine tune" a desired time course of response.

As used herein the term "modified vitamin D compound" encompasses any vitamin D compound in which one or more of the hydroxy functions present in such a compound are modified by derivatization with a hydrolyzable group. A "hydrolyzable group" is a hydroxy-modifying group that can be hydrolyzed in vivo, so as to regenerate the free hydroxy functions.

In the context of this disclosure, the term hydrolyzable group preferably includes acyl and hydrocarbyloxycarbonyl groups, i.e. groups of the type Q^1CO— and Q^2—O—CO, respectively, where Q^1 and Q^2 have the meaning defining earlier.

Structurally, the modified vitamin D compounds encompassed may be represented by the formula XI shown below:

XI



where Y_1, Y_2, and R are as previously defined herein with respect to formula I with the exception that R^5 in the side chain is —OY_3 and Y_3 is an acyl group or a hydrocarbyloxycarbonyl group, as previously defined herein.

Some specific examples of such modified vitamin D compounds include 2-propylidene-19-nor vitamin D derivatives such as:

2-(3'-hydroxypropylidene)-19-nor-1α,25$(OH)_2$-D_3-1,3, 25-Triacetate where Y_1=Y_2=Y_3 and is CH_3CO;

2-(3'-hydroxypropylidene)-19-nor-1α,25$(OH)_2$-D_3-1,3, 25-Trihexanoate where Y_1=Y_2=Y_3 and is $CH_3(CH_2)_4CO$;

2-(3'-hydroxypropylidene)-19-nor-1α,25$(OH)_2$-D_3-1,3, 25-Trinonanoate where Y_1=Y_2=Y_3 and is $CH_3(CH_2)_7CO$;

2-(3'-hydroxypropylidene)-19-nor-1α,25$(OH)_2$-D_3-25-Acetate where Y_1=Y_2 and is H and Y_3 is CH_3CO.

These compounds can be prepared by known methods. See for example U.S. Pat. No. 5,843,927.

Biological Activity of 2-Propylidene-19-nor-vitamin D Compounds

FIGS. **1** and **2**—Competitive VDR Binding

Competitive binding of the analogs to the porcine intestinal receptor was carried out by the method described by Dame et al (Biochemistry 25, 4523-4534, 1986), except the recombinantly produced rat receptor was used as the receptor (see Vanhooke et al., Biochemistry, in press, 2004).

FIG. **3**—HL-60 Cell Differentiation

The differentiation of HL-60 promyelocytic into monocytes was determined as described by Ostrem et al (J. Biol. Chem. 262, 14164-14171, 1987).

FIG. **4**—Transcription Activation

Transcriptional activity was measured in ROS 17/2.8 (bone) cells that were stably transfected with a 24-hydroxylase (24OHase) gene promoter upstream of a luciferase reporter gene (Arbour et al., 1998). Cells were given a range of doses. Sixteen hours after dosing the cells were harvested and luciferase activities were measured using a luminometer.

"RLU" in FIG. **4** refers to relative luciferase units.

FIGS. **5** and **6**—Intestinal Calcium Transport and Bone Calcium Mobilization

Male, weanling Sprague-Dawley rats were placed on Diet 11 (0.47% Ca) diet+AEK for one week followed by Diet 11 (0.02% Ca)+AEK for 3 weeks. The rats were then switched to a diet containing 0.47% Ca for one week followed by two weeks on a diet containing 0.02% Ca. Dose administration began during the last week on 0.02% calcium diet. Four consecutive ip doses were given approximately 24 hours apart. Twenty-four hours after the last dose, blood was collected from the severed neck and the concentration of serum calcium determined as a measure of bone calcium mobilization. The first 10 cm of the intestine was also collected for intestinal calcium transport analysis using the everted gut sac method.

Interpretation of Biological Data

FIG. **1** illustrates the relative activity of 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$ (also herein referred to as "F-Wit") and 1α,25-dihydroxyvitamin D_3 in binding to the 1α,25-dihydroxyvitamin D pig intestinal nuclear receptor. FIG. **2** illustrates the relative activity of the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (also herein referred to as "1AGR"), the Z-isomer of 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (also herein referred to as "2AGR"), the E-isomer of 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2D_3$ (also herein referred to as "1AGS"), the Z-isomer of 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2D_3$ (also herein referred to as "2AGS"), and 1α,25-dihydroxyvitamin D_3 in binding to the 1α,25-dihydroxyvitamin D pig intestinal nuclear receptor. FIGS. **1** and **2** show that F-Wit, 1AGR, 2AGR, 1AGS and 2AGS are all very active in binding to the 1α,25-hydroxyvitamin D_3 rat receptor.

The 2-propylidene-19-nor compounds of this invention exhibit a pattern of biological activity having high potency in promoting the differentiation of malignant cells, relatively high intestinal calcium transport activity and a relatively high ability to mobilize calcium from bone. This is illustrated by the biological assay results obtained for F-Wit, 1AGR, 2AGR, 1AGS and 2AGS which is summarized in FIGS. **3** through **6**. FIG. **3** shows a comparison of the activity of the known active metabolite 1α,25-dihydroxyvitamin D_3 as well as the analog 2-methylene-19-nor-(20S)-1,25$(OH)_2$ D_3 (also herein referred to as "2MD") and the presently claimed F-Wit, 1AGR and 1AGS analogs in inducing the differentiation of human leukemia cells (HL-60 cells) in culture to monocytes. Differentiation activity was assessed by a standard differentiation assay, abbreviated as NBT reduction (nitroblue tetrazolium reduction). The assay was conducted according to known procedures, as given, for example, by DeLuca et al U.S. Pat. No. 4,717,721 and Ostrem et al, J. Biol. Chem. 262, 14164, 1987. For the assay, the differentiation activity of the test compounds is expressed in terms of the percent of HL-60 cells having differentiated to normal cells in response to a given concentration of test compound.

The results summarized in FIG. **3** clearly show that the analogs, F-Wit, 1AGR and 1AGS are all as potent as 1α,25-dihydroxyvitamin D_3 and 2MD in promoting the differentiation of leukemia cells. Thus, in the NBT assay close to 90% of the cells are induced to differentiate by 1α,25-dihydroxyvitamin D_3 at a concentration of 1×10^{-7}M, and the same degree of differentiation is achieved by the F-Wit, 1AGR and 1AGS analogs at 1×10^{-7}M.

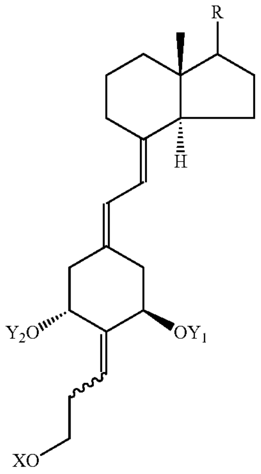
FIG. **4** illustrates that F-Wit, 1AGR and 1AGS all have significant transcriptional activity in bone cells. This result, together with the cell differentiation activity of FIG. **3**, suggests that the presently claimed 2-propylidene compounds of structure I, and particularly F-Wit, 1AGR and

1AGS, will be very effective in psoriasis because they have direct cellular activity in causing cell differentiation and in suppressing cell growth. These data also indicate that the presently claimed 2-propylidene compounds of structure I, and particularly F-Wit, 1AGR and 1AGS may have significant activity as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer.

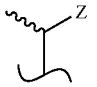
FIGS. **5** and **6** show a comparison of the calcemic activity of the known active 19-nor analog 2MD and the presently claimed F-Wit, 1AGR and 1AGS analogs. FIG. **5** shows that F-Wit, 1AGR and 1AGS all have relatively high intestinal calcium transport activity, and are more active than 2MD in intestinal calcium transport activity. Also, FIG. **6** shows that F-Wit, 1AGR and 1AGS all have significant ability to mobilize calcium from bone, and are less active in this regard than 2MD. Thus, in summary, the 2-propylidene-19-nor-analogs of structure I, and particularly F-Wit, 1AGR and 1AGS, show a selective activity profile combining high potency in inducing the differentiation of malignant cells, relatively high intestinal calcium transport activity and moderate bone calcium mobilization activity.

What is claimed is:

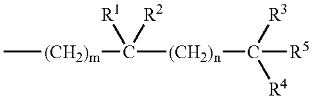
1. A compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where X may be an alkyl, hydrogen, hydroxy-protecting group, hydroxyalkyl, alkoxyalkyl and aryloxyalkyl, and where the group r is represented by the structure:



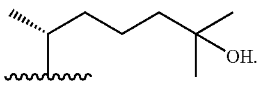
where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH_2OY, —C≡CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



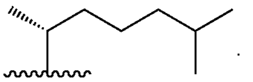
$$-(CH_2)_m-\overset{R^1\ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group $-(CH_2)_p-$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $-(CH_2)_q-$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $-CH(CH_3)-$, $-(CH_2)m-$, $-(CH_2)n-$, or $-(CR_1R_2)-$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

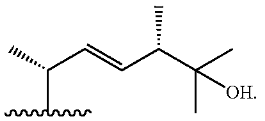
2. The compound of claim **1** where R is a side chain of the formula



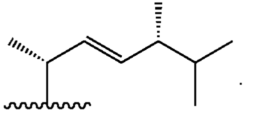
3. The compound of claim **1** where R is a side chain of the formula



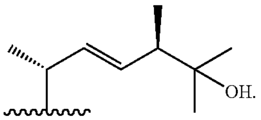
4. The compound of claim **1** where R is a side chain of the formula



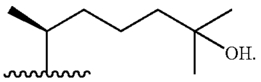
5. The compound of claim **1** where R is a side chain of the formula



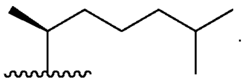
6. The compound of claim **1** where R is a side chain of the formula



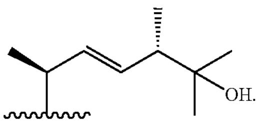
7. The compound of claim **1** where R is a side chain of the formula



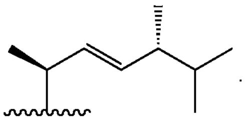
8. The compound of claim **1** where R is a side chain of the formula



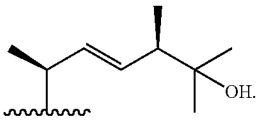
9. The compound of claim **1** where R is a side chain of the formula



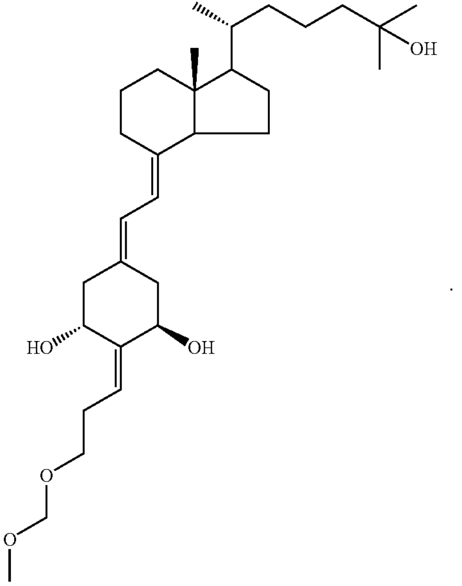
10. The compound of claim **1** where R is a side chain of the formula



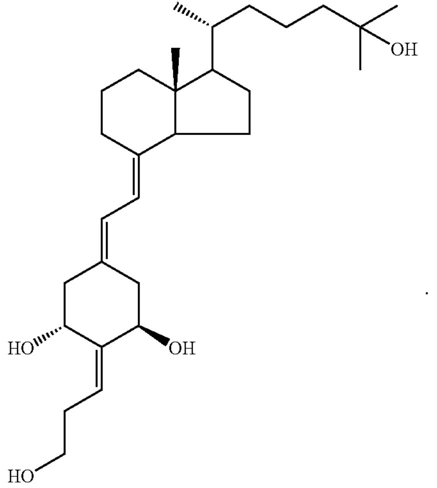
11. The compound of claim **1** where R is a side chain of the formula



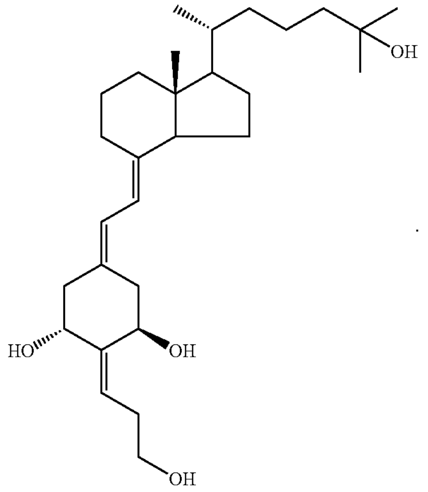
12. 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$ having the formula:



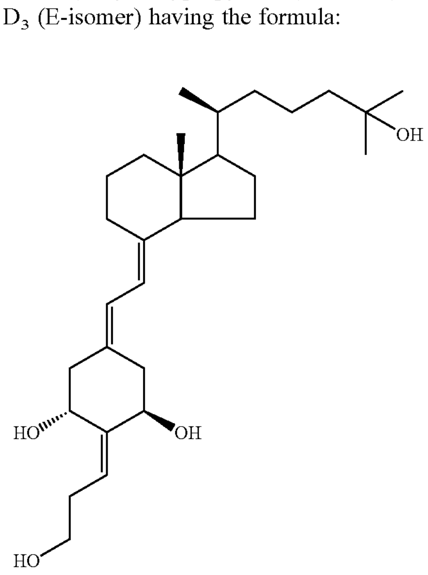
13. 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (E-isomer) having the formula:



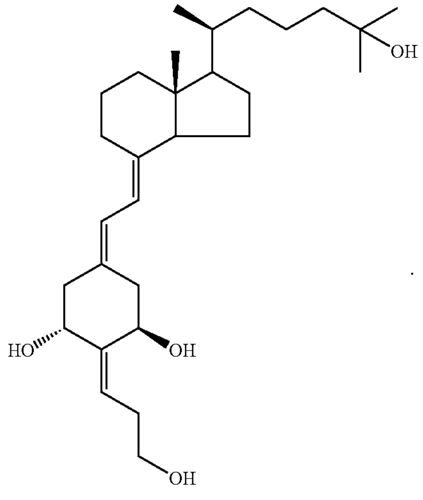
14. 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (Z-isomer) having the formula:



15. 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2$ D_3 (E-isomer) having the formula:



16. 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2$ D_3 (Z-isomer) having the formula:



17. A pharmaceutical composition containing an effective amount of at least one compound as claimed in claim **1** together with a pharmaceutically acceptable excipient.

18. The pharmaceutical composition of claim **17** wherein said effective amount comprises from about 0.01 μg to about 100 μg per gram of composition.

19. The pharmaceutical composition of claim **17** wherein said effective amount comprises from about 0.1 μg to about 50 μg per gram of composition.

20. The pharmaceutical composition containing 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$ in an amount from about 0.01 μg to about 100 μg per gram of composition.

21. The pharmaceutical composition of claim **20** containing 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$ in an amount from about 0.1 μg to about 50 μg per gram compositon.

22. The pharmaceutical composition of claim **17** containing 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (E-isomer) in an amount from about 0.01 μg to about 100 μg.

23. The pharmaceutical composition of claim **17** containing 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (E-isomer) in an amount from about 0.1 μg to about 50 μg.

24. The pharmaceutical composition of claim **17** containing 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (Z-isomer) in an amount from about 0.01 μg to about 100 μg.

25. The pharmaceutical composition of claim **17** containing 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (Z-isomer) in an amount from about 0.1 μg to about 50 μg.

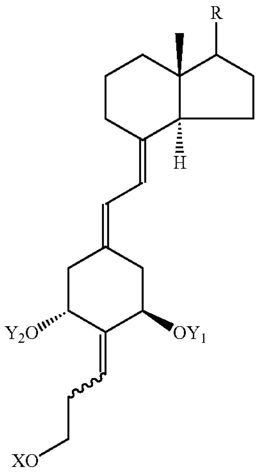
26. The pharmaceutical composition of claim **17** containing 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2$ D_3 (E-isomer) in an amount from about 0.01 μg to about 100 μg.

27. The pharmaceutical composition of claim **17** containing 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2$ D_3 (E-isomer) in an amount from about 0.1 μg to about 50 μg.

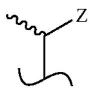
28. The pharmaceutical composition of claim **17** containing 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2$ D_3 (Z-isomer) in an amount from about 0.01 μg to about 100 g.

29. The pharmaceutical composition of claim **17** containing 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2$ D_3 (Z-isomer) in an amount from about 0.1 μg to about 50 μg.

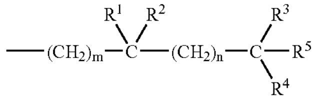
30. A method of treating metabolic bone disease where it is desired to maintain or increase bone mass comprising administering to a patient with said disease an effective amount of a compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where X may be an alkyl, hydrogen, hydroxy-protecting group, hydroxyalkyl, alkoxyalkyl and aryloxyalkyl, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from the Y, —OY, —CH_2OY, —C≡CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C$_{1-5}$-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C$_{1-5}$ alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group —(CH$_2$)$_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —(CH$_2$)$_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C$_{1-5}$ alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —CH(CH$_3$)—, —(CH$_2$)$_m$—, (CH$_2$)$_n$ or —(CR$_1$R$_2$)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

31. The method of claim **30** where the disease is senile osteoporosis.

32. The method of claim **30** where the disease is postmenopausal osteoporosis.

33. The method of claim **30** where the disease is steroid-induced osteoporosis.

34. The method of claim **30** where the disease is low bone turnover osteoporosis.

35. The method of claim **30** where the disease is osteomalacia.

36. The method of claim **30** where the disease is renal osteodystrophy.

37. The method of claim **30** wherein the compound is administered orally.

38. The method of claim **30** wherein the compound is administered parenterally.

39. The method of claim **30** wherein the compound is administered transdermally.

40. The method of claim **30** wherein the compound is administered in a dosage of from 0.01 μg to 100 μg per day.

41. The method of claim **30** wherein the compound is 2-(3'-methoxymethoxy)propylidene)-19-nor-1α,25-(OH)$_2$ D$_3$.

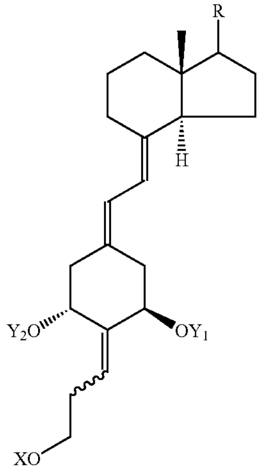
42. The method of claim **30** wherein the compound is 2-(3'-hydroxypropylidene)-19-nor-1α,25-(OH)$_2$D$_3$ (E-isomer).

43. The method of claim **30** wherein the compound is 2-(3'-hydroxypropylidene)-19-nor-1α,25-(OH)$_2$D$_3$ (Z-isomer).

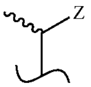
44. The method of claim **30** wherein the compound is 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-(OH)$_2$D$_3$ (E-isomer).

45. The method of claim **30** wherein the compound is 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-(OH)$_2$D$_3$ (Z-isomer).

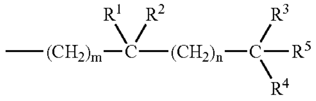
46. A method of treating psoriasis comprising administering to a patient with psoriasis an effective amount of a compound having the formula:



where Y$_1$ and Y$_2$, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where X may be an alkyl, hydrogen, hydroxy-protecting group, hydroxyalkyl, alkoxyalkyl and aryloxyalkyl, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from the Y, —OY, —CH$_2$OY, —C≡CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C$_{1-5}$-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C$_{1-5}$ alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group —(CH$_2$)$_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —(CH$_2$)$_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C$_{1-5}$ alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —$CH(CH_3)$—, —$(CH_2)_m$—, $(CH_2)_n$ or —(CR_1R_2)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

47. The method of claim **46** wherein the compound is administered orally.

48. The method of claim **46** wherein the compound is administered parenterally.

49. The method of claim **46** wherein the compound is administered transdermally.

50. The method of claim **46** wherein the compound is administered topically.

51. The method of claim **46** wherein said effective amount comprises about 0.01 μg/day to about 100 μg/day of said compound.

52. The method of claim **46** wherein the compound is 2-[3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2$ D_3.

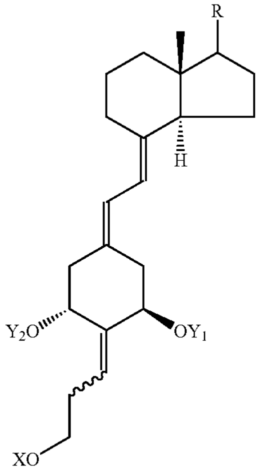
53. The method of claim **46** wherein the compound is 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (E-isomer).

54. The method of claim **46** wherein the compound is 2-(3'-hydroxypropylidene)-19-nor-1α,25-$(OH)_2D_3$ (Z-isomer).

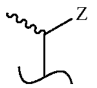
55. The method of claim **46** wherein the compound is 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2D_3$ (E-isomer).

56. The method of claim **46** wherein the compound is 2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-$(OH)_2D_3$ (Z-isomer).

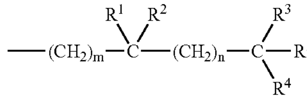
57. A method of treating leukemia, colon cancer, breast cancer, skin cancer or prostate cancer comprising administering to a patient an effective amount of a compound having the formula:



where Y_1 and Y_2 which the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where X may be an alkyl, hydrogen, hydroxy-protecting group, hydroxyalkyl, alkoxyalkyl and aryloxyalkyl, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH_2OY, —C≡CY and —CH=CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ R^2}{\overset{\diagdown\diagup}{C}}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group —$(CH_2)_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —$(CH_2)_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —$CH(CH_3)$—, —$(CH_2)_m$—, —$(CH_2)_n$— or (CR_1R_2)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

58. The method of claim **57** wherein the compound is administered orally.

59. The method of claim **57** wherein the compound is administered parenterally.

60. The method of claim **57** wherein the compound is administered transdermally.

61. The method of claim **57** wherein the compound is administered in a dosage of from about 0.01 μg/day to about 100 μg/day.

62. The method of claim **57** wherein the compound is 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2$ D_3.

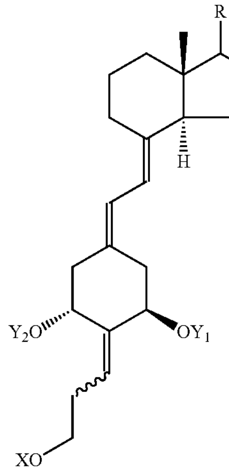
63. The method of claim **57** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-1α,25-$(OH)_2D_3$ (E-isomer).

64. The method of claim **57** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-1α,25-$(OH)_2D_3$ (Z-isomer).

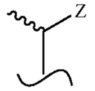
65. The method of claim **57** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-(20S)-1α,25-$(OH)_2D_3$ (E-isomer).

66. The method of claim **57** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-(20S)-1α,25-$(OH)_2D_3$ (Z-isomer).

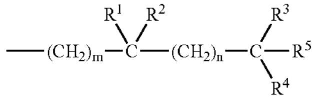
67. A method of increasing the strength of a bone comprising administering to a patient in need of such treatment an effective amount of a compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where X may be an alkyl, hydrogen, hydroxy-protecting group, hydroxyalkyl, alkoxyalkyl, and aryloxyalkyl and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH_2OY, —C≡CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$—(CH_2)_m—\overset{R^1\ R^2}{C}—(CH_2)_n—\underset{R^4}{\overset{R^3}{C}}—R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $═CR^2R^3$, or the group $—(CH_2)_p—$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $—(CH_2)_q—$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $—CH(CH_3)—$, $—(CH_2)_m—$, $—(CH_2)_n—$ or $(CR_1R_2)—$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

68. The method of claim **67** wherein the bone strength is cortical strength.

69. The method of claim **67** wherein the bone strength is trabecular strength.

70. The method of claim **67** wherein the compound is administered orally.

71. The method of claim **67** wherein the compound is administered parenterally.

72. The method of claim **67** wherein the compound is administered transdermally.

73. The method of claim **67** wherein the compound is administered in a dosage of from 0.01 μg to 100 μg per day.

74. The method of claim **67** wherein the compound is 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$.

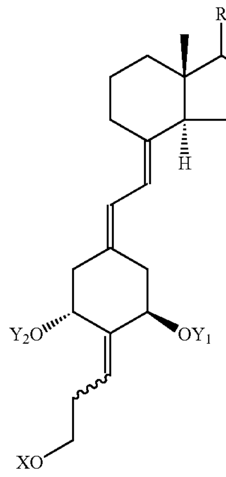
75. The method of claim **67** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-1α,25-$(OH)_2D_3$ (E-isomer).

76. The method of claim **67** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-1α,25-$(OH)_2D_3$ (Z-isomer).

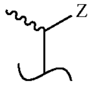
77. The method of claim **67** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-(20S)-1α,25-$(OH)_2D_3$ (E-isomer).

78. The method of claim **67** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-(20S)-1α,25-$(OH)_2D_3$ (Z-isomer).

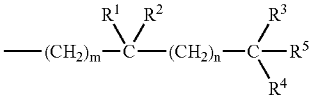
79. A method of treating an autoimmune disease comprising administering to a patient with said disease an effective amount of a compound having the formula



where Y_1 and Y_2 which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where X may be an alkyl, hydrogen, hydroxy-protecting group, hydroxyalkyl, alkoxyalkyl and aryloxyalkyl, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH$_2$OY, —C≡CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$—(CH_2)_m—\overset{R^1\ \ R^2}{C}—(CH_2)_n—\underset{R^4}{\overset{R^3}{C}}—R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C$_{1-5}$-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C$_{1-5}$ alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, ═CR^{2}R^3, or the group —(CH$_2$)$_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —(CH$_2$)$_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C$_{1-5}$ alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —CH(CH$_3$)—, —(CH$_2$)m—, —(CH$_2$)n—, or —CR$_1$R$_2$)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

80. The method of claim **79** where the disease is multiple sclerosis.

81. The method of claim **79** where the disease is diabetes mellitus.

82. The method of claim **79** where the disease is lupus.

83. The method of claim **79** wherein the compound is administered orally.

84. The method of claim **79** wherein the compound is administered parenterally.

85. The method of claim **79** wherein the compound is administered transdermally.

86. The method of claim **79** wherein the compound is administered in a dosage of from about 0.01 μg/day to about 100 μg/day.

87. The method of claim **79** wherein the compound is 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-(OH)$_2$D$_3$.

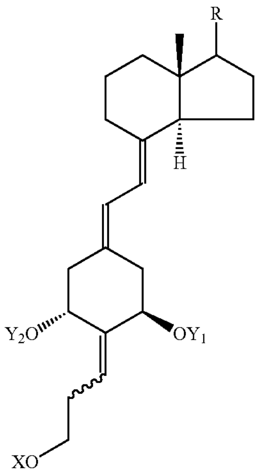
88. The method of claim **79** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-1α,25-(OH)$_2$D$_3$ (E-isomer).

89. The method of claim **79** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-1α,25-(OH)$_2$D$_3$ (Z-isomer).

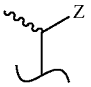
90. The method of claim **79** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-(20S)-1α,25-(OH)$_2$D$_3$ (E-isomer).

91. The method of claim **79** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-(20S)-1α,25-(OH)$_2$D$_3$ (Z-isomer).

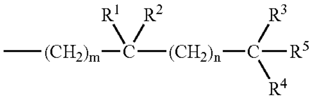
92. A method of treating an inflammatory bowel disease comprising administering to a patient with said disease an effective amount of a compound having the formula



where Y$_1$ and Y$_2$ which the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where X may be an alkyl, hydrogen, hydroxy-protecting group, hydroxyalkyl, alkoxyalkyl and aryloxyalkyl, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH$_2$OY, —C≡—CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$—(CH_2)_m—\overset{R^1\ \ R^2}{C}—(CH_2)_n—\underset{R^4}{\overset{R^3}{C}}—R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C$_{1-5}$-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C$_{1-5}$ alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, ═CR^{2}R^3, or the group —(CH$_2$)$_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —$(CH_2)_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —$CH(CH_3)$—, —(CH_2)m—, —(CH_2)n—, or —CR_1R_2)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

93. The method of claim **92** wherein the disease is Crohn's disease.

94. The method of claim **92** wherein the disease is ulcerative colitis.

95. The method of claim **92** wherein the compound is administered orally.

96. The method of claim **92** wherein the compound is administered parenterally.

97. The method of claim **92** wherein the compound is administered transdermally.

98. The method of claim **92** wherein the compound is administered in a dosage of from about 0.01 μg/day to about 100 μg/day.

99. The method of claim **92** wherein the compound is 2-[(3'-methoxymethoxy)propylidene]-19-nor-1α,25-$(OH)_2D_3$.

100. The method of claim **92** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-1α,25-$(OH)_2D_3$ (E-isomer).

101. The method of claim **92** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-1α,25-$(OH)_2D_3$ (Z-isomer).

102. The method of claim **92** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-(20S)-1α,25-$(OH)_2D_3$ (E-isomer).

103. The method of claim **92** wherein the compound is 2-[(3'-hydroxypropylidene]-19-nor-(20S)-1α,25-$(OH)_2D_3$ (Z-isomer).

* * * * *

Exhibit H

US 20050227950A1

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DeLuca et al. (43) **Pub. Date: Oct. 13, 2005**

(54) 2-ALKYLIDENE-18,19-DINOR-VITAMIN D COMPOUNDS

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(51) **Int. Cl.**^{7} **A61K 31/59**; C07C 401/00

(52) **U.S. Cl.** **514/167**; 552/653

(57) ABSTRACT

2-alkylidene-18,19-dinor-vitamin D compounds are disclosed as well as pharmaceutical uses for these compounds and methods of synthesizing these compounds. These compounds are characterized by low bone calcium mobilization activity and high intestinal calcium transport activity. This results in novel therapeutic agents for the treatment and prophylaxis of diseases where bone formation is desired, particularly osteoporosis, as well as autoimmune diseases such as multiple sclerosis, diabetes mellitus and lupus. These compounds also exhibit pronounced activity in arresting the proliferation of undifferentiated cells and inducing their differentiation to the monocyte thus evidencing use as an anti-cancer agent and for the treatment of skin diseases such as psoriasis. These compounds also increase both breaking strength and crushing strength of bones evidencing use in conjunction with bone replacement surgery such as hip and knee replacements.

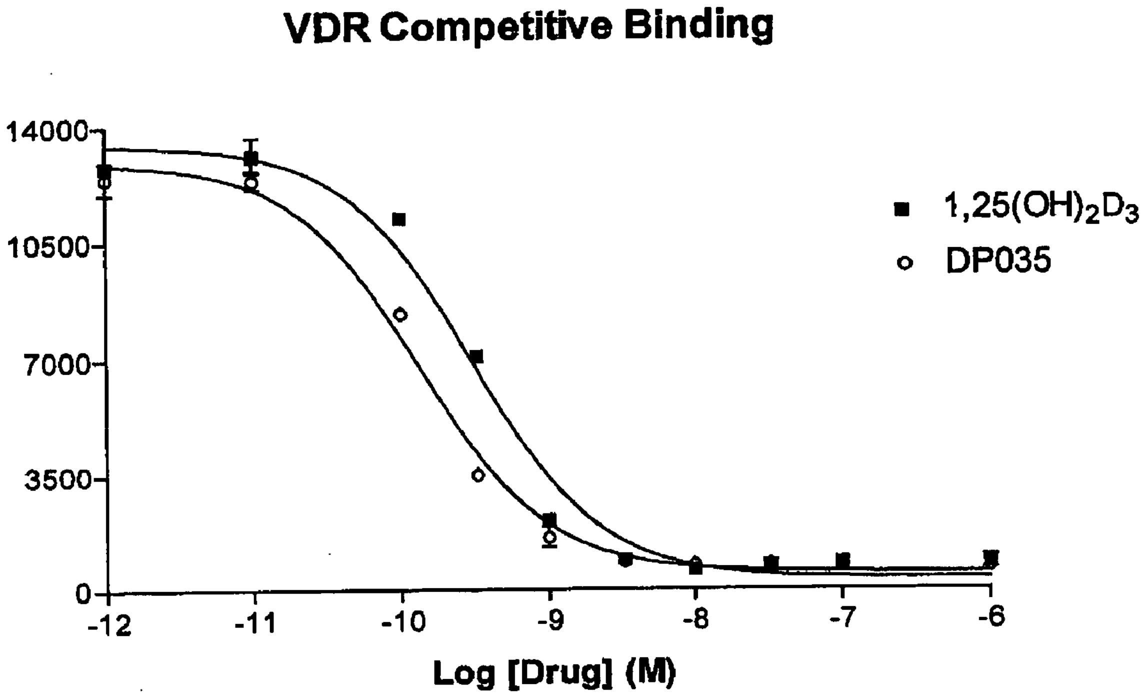

VDR Competitive Binding
14000
10500
7000
3500
0
-12
-11
-10
-9
-8
-7
-6
Log [Drug] (M)
■ $1,25(OH)_2D_3$
○ DP035

Figure 1

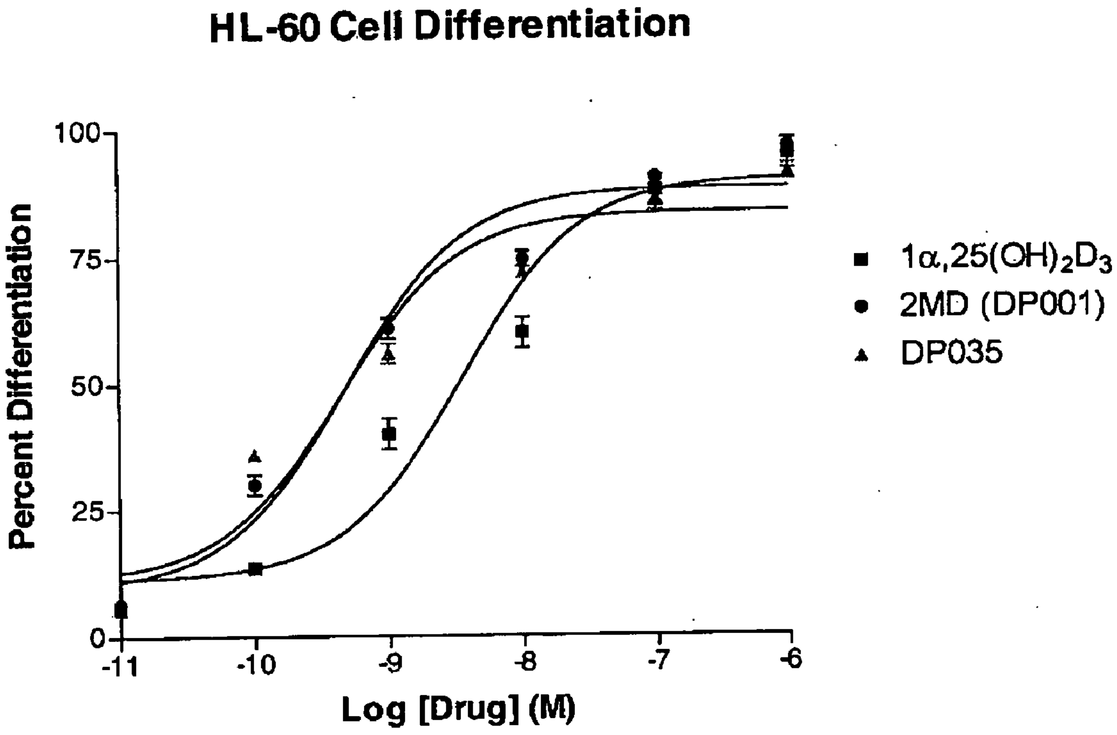

HL-60 Cell Differentiation
Percent Differentiation
100
75
50
25
0
-11
-10
-9
-8
-7
-6
Log [Drug] (M)
■ 1α,25(OH)2D3
● 2MD (DP001)
▲ DP035

Figure 2

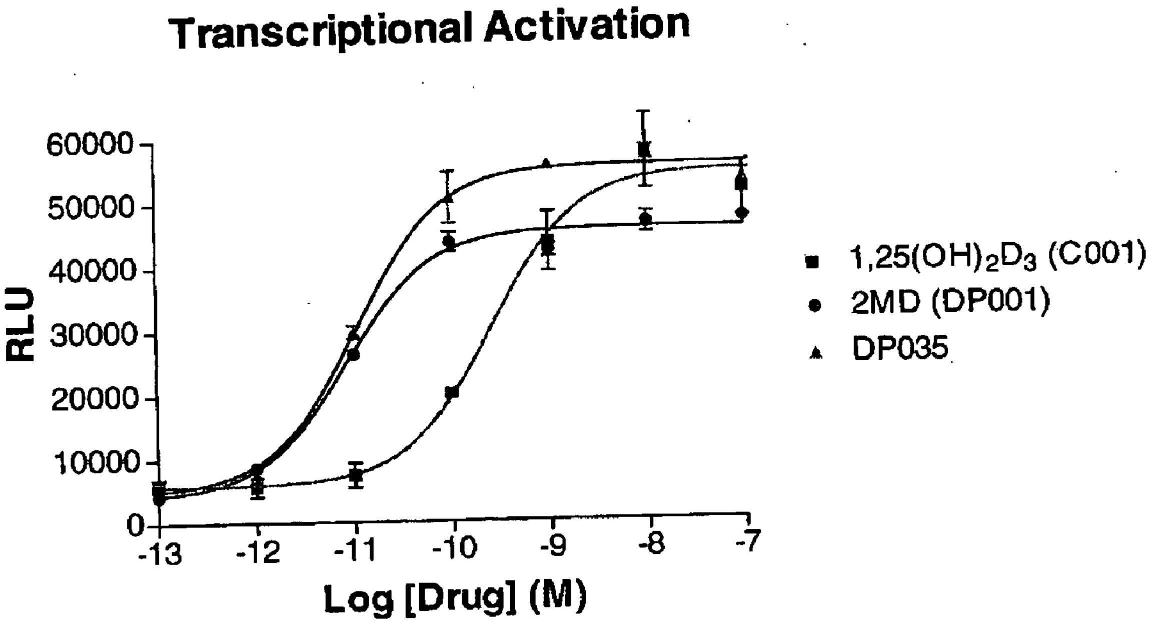

Transcriptional Activation
60000
50000
40000
30000
20000
10000
0
RLU
-13
-12
-11
-10
-9
-8
-7
Log [Drug] (M)
■ 1,25(OH)2D3 (C001)
● 2MD (DP001)
▲ DP035

Figure 3

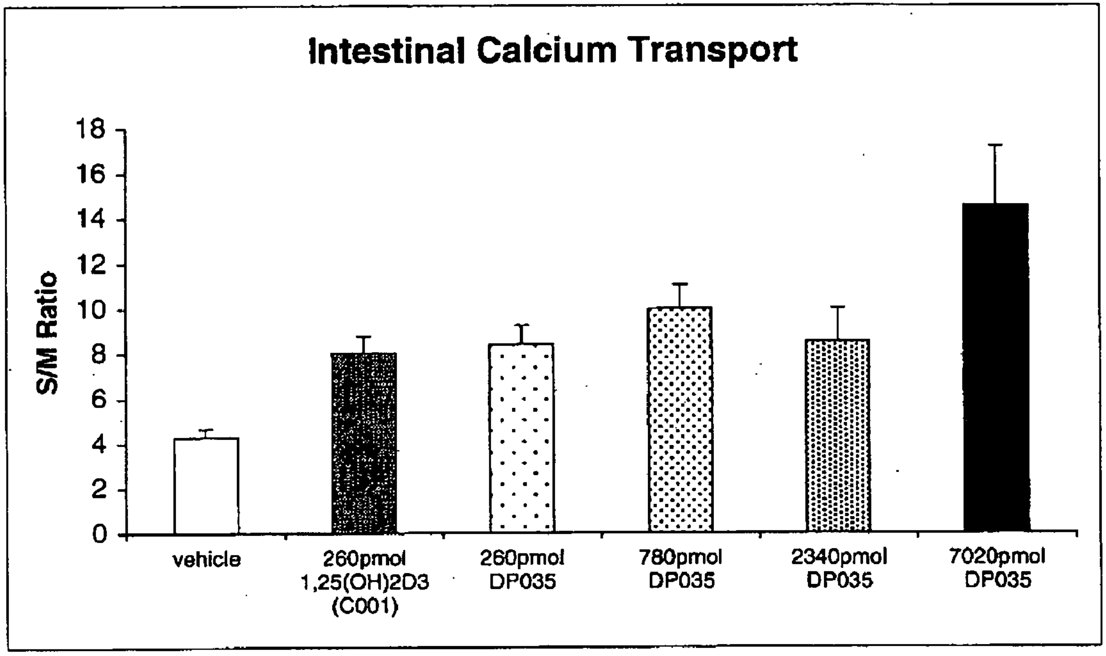

Intestinal Calcium Transport
S/M Ratio
18
16
14
12
10
8
6
4
2
0
vehicle
260pmol 1,25(OH)2D3 (C001)
260pmol DP035
780pmol DP035
2340pmol DP035
7020pmol DP035

Figure 4

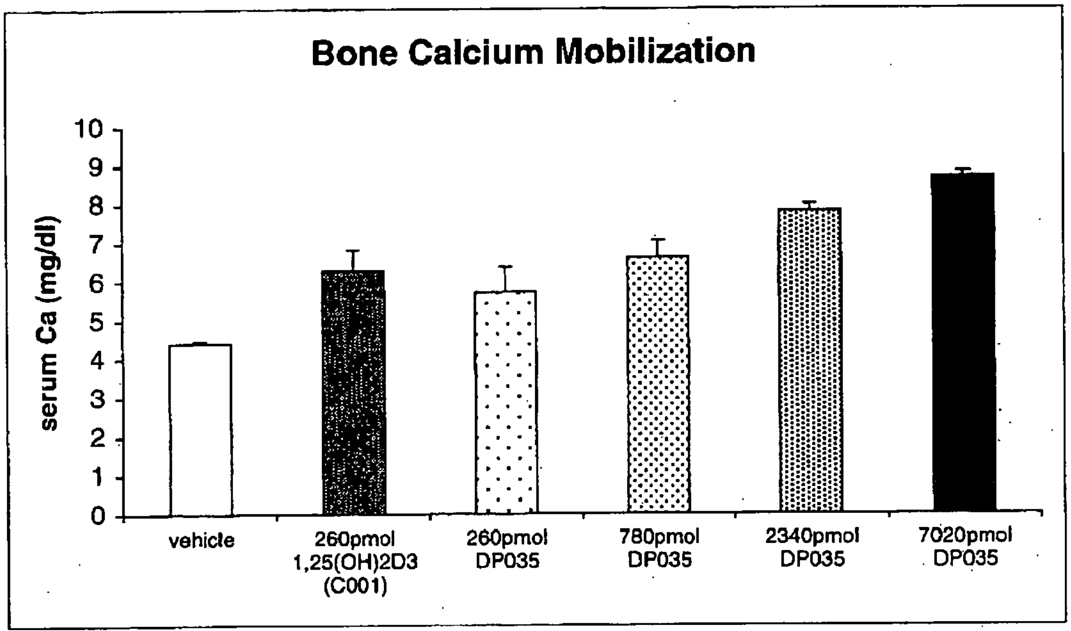

Bone Calcium Mobilization
serum Ca (mg/dl)
10
9
8
7
6
5
4
3
2
1
0
vehicle
260pmol 1,25(OH)2D3 (C001)
260pmol DP035
780pmol DP035
2340pmol DP035
7020pmol DP035

Figure 5

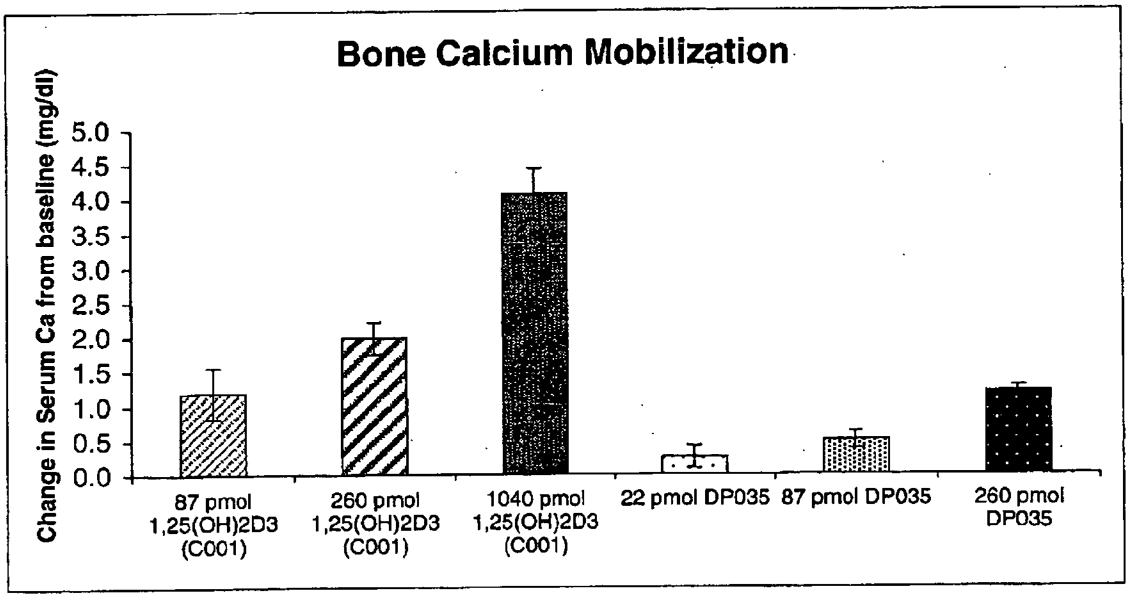

Bone Calcium Mobilization
Change in Serum Ca from baseline (mg/dl)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
87 pmol 1,25(OH)2D3 (C001)
260 pmol 1,25(OH)2D3 (C001)
1040 pmol 1,25(OH)2D3 (C001)
22 pmol DP035
87 pmol DP035
260 pmol DP035

Figure 6

2-ALKYLIDENE-18,19-DINOR-VITAMIN D COMPOUNDS

BACKGROUND OF THE INVENTION

[0001] This invention relates to vitamin D compounds, and more particularly to 2-alkylidene- 18,19-dinor-vitamin D compounds, pharmaceutical uses for these compounds and a general method for chemically synthesizing these compounds.

[0002] The natural hormone, 1α,25-dihydroxyvitamin D_3 and its analog in the ergosterol series, i.e. 1α,25-dihydroxyvitamin D_2 are known to be highly potent regulators of calcium homeostasis in animals and humans, and their activity in cellular differentiation has also been established, Ostrem et al., Proc. Natl. Acad. Sci. USA, 84, 2610 (1987). Many structural analogs of these metabolites have been prepared and tested, including 1α-hydroxyvitamin D_3, 1α-hydroxyvitamin D_2, various side chain homologated vitamins and fluorinated analogs. Some of these compounds exhibit an interesting separation of activities in cell differentiation and calcium regulation. This difference in activity may be useful in the treatment of a variety of diseases as renal osteodystrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies.

[0003] A particularly interesting class of vitamin D analogs are referred to as the 19-nor-vitamin D compounds. The 19-nor-vitamin D compounds are characterized by the replacement of the A-ring exocyclic methylene group (carbon 19), typical of the vitamin D system, by two hydrogen atoms. Biological testing of such 19-nor-analogs (e.g., 1α,25-dihydroxy-19-nor-vitamin D_3) revealed a selective activity profile with high potency in inducing cellular differentiation, and very low calcium mobilizing activity. Thus, these compounds are potentially useful as therapeutic agents for the treatment of malignancies, or the treatment of various skin disorders. Two different methods of synthesis of such 19-nor-vitamin D analogs have been described (Perlman et al., Tetrahedron Lett. 31, 1823 (1990); Perlman et al., Tetrahedron Lett. 32, 7663 (1991), and DeLuca et al., U.S. Pat. No. 5,086,191).

[0004] In U.S. Pat. No. 4,666,634, 2β-hydroxy and alkoxy (e.g., ED-71) analogs of 1α,25-dihydroxyvitamin D_3 have been described and examined by Chugai group as potential drugs for osteoporosis and as antitumor agents. See also Okano et al., Biochem. Biophys. Res. Commun. 163, 1444 (1989). Other 2-substituted (with hydroxyalkyl, e.g., ED-120, and fluoroalkyl groups) A-ring analogs of 1α,25-dihydroxyvitamin D_3 have also been prepared and tested (Miyamoto et al., Chem. Pharm. Bull. 41, 1111 (1993); Nishii et al., Osteoporosis Int. Suppl. 1, 190 (1993); Posner et al., J. Org. Chem. 59, 7855 (1994), and J. Org. Chem. 60, 4617 (1995)).

[0005] Recently, 2-substituted analogs of 1α,25-dihydroxy-19-nor-vitamin D_3 have also been synthesized, i.e. compounds substituted at the 2-position of the A-ring with hydroxy or alkoxy groups (DeLuca et al., U.S. Pat. No. 5,536,713), with 2-alkyl groups (DeLuca et al U.S. Pat. No. 5,945,410), and with 2-alkylidene groups (DeLuca et al U.S. Pat. No. 5,843,928), which exhibit interesting and selective activity profiles. All these studies indicate that binding sites in vitamin D receptors can accommodate different substituents at C-2 in the synthesized vitamin D analogs.

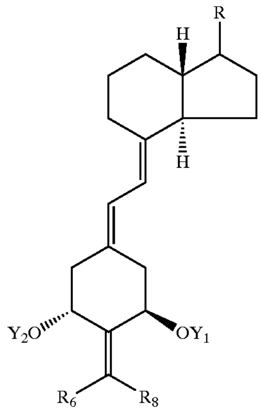
[0006] Another class of known vitamin D compounds are the 18,19-dinor analogs. These analogs have both the C-18 angular methyl substituent (carbon 18) normally attached to carbon 13 of the CD-ring structure and the C-19 exocyclic methylene group (carbon 19) normally attached to carbon 10 of the A-ring, which are typical of all vitamin D compounds, removed and replaced by hydrogen atoms. Reference should be made to the U.S. Pat. No. 5,843,927 as well as U.S. Pat. Nos. 5,756,489 and 5,721,225 for a more complete description of these compounds, their pharmaceutical uses, and their synthesis.

SUMMARY OF THE INVENTION

[0007] In a continuing effort to explore the 19-nor class of pharmacologically important vitamin D compounds, the present invention is directed toward 2-alkylidene-18,19-dinor-vitamin D analogs, various pharmaceutical uses for these compounds, and a general method for chemically synthesizing these compounds. In particular, the present invention is directed toward (20S)-2-methylene-1α,25-dihydroxy-18,19-dinor-vitamin D_3, its biological activity, and various pharmaceutical uses for this compound.

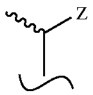
[0008] Structurally these novel 2-alkylidene-18,19-dinor-vitamin D analogs are characterized by the general formula I shown below:

I

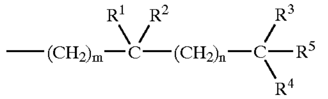


[0009] where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R_6 and R_8, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group —$(CH_2)_x$— where X is an integer from 2 to 5, and where the group R represents any of the typical side chains known for vitamin D type compounds.

[0010] More specifically R can represent a saturated or unsaturated hydrocarbon radical of 1 to 35 carbons, that may be straight-chain, branched or cyclic and that may contain one or more additional substituents, such as hydroxy- or protected-hydroxy groups, fluoro, carbonyl, ester, epoxy, amino or other heteroatomic groups. Preferred side chains of this type are represented by the structure below



[0011] where the stereochemical center (corresponding to C-20 in steroid numbering) may have the R or S configuration, (i.e. either the natural configuration about carbon 20 or the 20-epi configuration), and where Z is selected from Y, —OY, —CH_2OY, —C≡CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



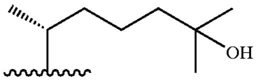
$$-(CH_2)_m-\overset{R^1\ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

[0012] where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, ═CR^2R^3, or the group —$(CH_2)_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —$(CH_2)_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —$CH(CH_3)$—, —$(CH_2)_m$—, $(CH_2)_n$, or —CR^1R^2— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

[0013] The wavy line to the methyl substituent at C-20 indicates that carbon 20 may have either the R or S configuration, i.e. the natural configuration (20R) or the unnatural 20-epi configuration (20S).

[0014] Specific important examples of side chains with natural 20R-configuration are the structures represented by formulae (a), b), (c), (d) and (e) below. i.e. the side chain as it occurs in 25-hydroxyvitamin D_3 (a); vitamin D_3 (b); 25-hydroxyvitamin D_2 (c); vitamin D_2 (d); and the C-24 epimer of 25-hydroxyvitamin D_2 (e):

(a)



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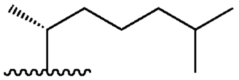
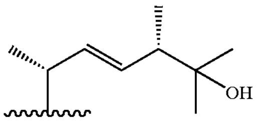
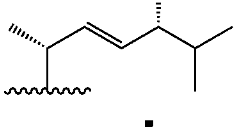
(b)



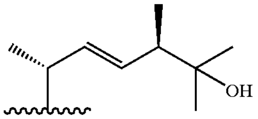
(c)



(d)



(e)



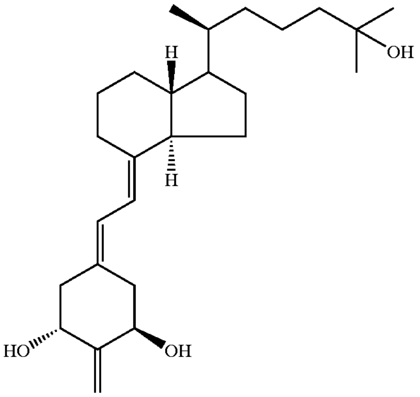
[0015] The above novel 2-alkylidene- 18,19-dinor vitamin D compounds exhibit a desired, and highly advantageous, pattern of biological activity. These compounds are characterized by relatively high intestinal calcium transport activity, i.e. similar to that of 1α,25-dihydroxyvitamin D_3, while also exhibiting relatively low activity, as compared to 1α,25-dihydroxyvitamin D_3, in their ability to mobilize calcium from bone. Hence, these compounds are highly specific in their calcemic activity. Their preferential activity on intestinal calcium transport and reduced calcium mobilizing activity allows the in vivo administration of these compounds for the treatment and prophylaxis of metabolic bone diseases where bone loss is a major concern. Because of their preferential calcemic activity on gut calcium transport, these compounds would be preferred therapeutic agents for the treatment and prophylaxis of diseases where bone formation is desired, such as osteoporosis, especially low bone turnover osteoporosis, steroid induced osteoporosis, senile osteoporosis or postmenopausal osteoporosis, as well as osteomalacia and renal osteodystrophy. The compounds may be administered transdermally, orally or parenterally. The compounds may be present in a pharmaceutical composition in an amount from about 0.01 μg/gm to about 100 μg/gm of the composition, preferably from about 0.1 μg/gm to about 50 μg/gm of the composition, and may be administered in dosages of from about 0.01 μg/day to about 100 μg/day, preferably from about 0.1 μg/day to about 50 μg/day.

[0016] The compounds of the invention are also especially suited for treatment and prophylaxis of human disorders which are characterized by an imbalance in the immune system, e.g. in autoimmune diseases, including multiple sclerosis, diabetes mellitus, lupus, host versus graft reaction, and rejection of transplants; and additionally for the treatment and prophylaxis of inflammatory diseases, such as rheumatoid arthritis, asthma, and inflammatory bowel diseases such as Crohn's disease or ulcerative colitis, as well as the improvement of bone fracture healing and improved bone grafts. It has also been discovered that these compounds increase breaking strength (cortical strength) as well as crushing strength (trabecular strength) of bones. Thus, these compounds could also be used in conjunction with bone replacement procedures such as hip replacements, knee replacements, and the like. Acne, alopecia, skin conditions such as dry skin (lack of dermal hydration), undue skin slackness (insufficient skin firmness), insufficient sebum secretion and wrinkles, and hypertension are other conditions which may be treated with the compounds of the invention.

[0017] The above compounds are also characterized by high cell differentiation activity. Thus, these compounds also provide therapeutic agents for the treatment of psoriasis, or as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer. The compounds may be present in a composition to treat psoriasis in an amount from about 0.01 μg/gm to about 100 μg/gm of the composition, preferably from about 0.01 μg/gm to about 50 μg/gm of the composition, and may be administered topically, transdermally, orally or parenterally in dosages of from about 0.01 μg/day to about 100 μg/day, preferably from about 0.1 μg/day to about 50 μg/day.

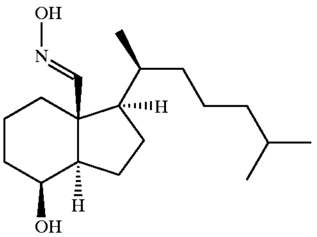
[0018] In particular, 2-methylene-18,19-dinor-(20S)-1α,25-dihydroxy-vitamin D_3 has been synthesized and its binding, transcriptional, calcemic (both intestinal calcium transport and bone calcium mobilization) and differentiation activities determined. Structurally this 18,19-dinor analog is characterized by the general formula Ia shown below:

Ia

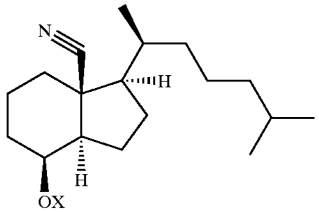


[0019] The invention also provides a novel synthesis for the production of the end products of formula I, and specifically of formula Ia. In addition, this invention provides novel intermediate compounds formed during the synthesis of the end products. Structurally, these novel intermediates are characterized by the general formulae IV, V, VI and VII, below where XI may be —H or —NO, and X^2 and X^3 may be —H or a hydroxy protecting group.

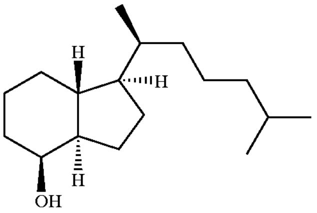
IV



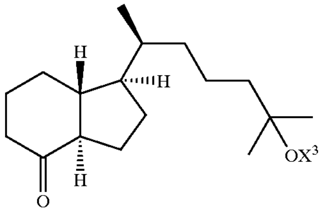
V



VI



VII



BRIEF DESCRIPTION OF THE DRAWINGS

[0020] **FIG. 1** is a graph illustrating the relative activity of 1α,25-dihydroxyvitamin D_3 (C001) as well as the herein described and claimed (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DP035) in binding to the 1α,25-dihydroxyvitamin D pig intestinal nuclear receptor;

[0021] **FIG. 2** is a graph illustrating the percent HL-60 cell differentiation as a function of the concentration of 1α,25-dihydroxyvitamin D_3 (C001), (20S)-2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 (2MD) and (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DP035);

[0022] **FIG. 3** is a graph illustrating the transcriptional activity as a function of the concentration of 1α,25-dihydroxyvitamin (C001), (20S)-2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 (2MD) and (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DPO35);

[0023] **FIG. 4** is a bar graph illustrating the intestinal calcium transport activity of (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DP035) at various dosages as compared to control (vehicle) and 1α,25-dihydroxyvitamin D_3 (C001);

[0024] **FIG. 5** is a bar graph illustrating the bone calcium mobilization activity of (20S)-2-methylene-18,19-dinor-1α, 25-dihydroxyvitamin D_3 (DP035) at various dosages as compared to control (vehicle) and 1α,25 -dihydroxyvitamin D_3 (C001); and

[0025] **FIG. 6** is a bar graph illustrating the bone calcium mobilization activity of (20S)-2-methylene-18,19-dinor-1α, 25-dihydroxyvitamin D_3 (DP035) as compared to 1α,25-dihydroxyvitamin D_3 (C001) at various dosages.

DETAILED DESCRIPTION OF THE INVENTION

[0026] As used in the description and in the claims, the term "hydroxy-protecting group" signifies any group commonly used for the temporary protection of hydroxy functions, such as for example, alkoxycarbonyl, acyl, alkylsilyl or alkylarylsilyl groups (hereinafter referred to simply as "silyl" groups), and alkoxyalkyl groups. Alkoxycarbonyl protecting groups are alkyl-O—CO— groupings such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or allyloxycarbonyl. The term "acyl" signifies an alkanoyl group of 1 to 6 carbons, in all of its isomeric forms, or a carboxyalkanoyl group of 1 to 6 carbons, such as an oxalyl, malonyl, succinyl, glutaryl group, or an aromatic acyl group such as benzoyl, or a halo, nitro or alkyl substituted benzoyl group. The word "alkyl" as used in the description or the claims, denotes a straight-chain or branched alkyl radical of 1 to 10 carbons, in all its isomeric forms. Alkoxyalkyl protecting groups are groupings such as methoxymethyl, ethoxymethyl, methoxyethoxymethyl, or tetrahydrofuranyl and tetrahydropyranyl. Preferred silyl-protecting groups are trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, dibutylmethylsilyl, diphenylmethylsilyl, phenyldimethylsilyl, diphenyl-t-butylsilyl and analogous alkylated silyl radicals. The term "aryl" specifies a phenyl-, or an alkyl-, nitro- or halo-substituted phenyl group.

[0027] A "protected hydroxy" group is a hydroxy group derivatised or protected by any of the above groups commonly used for the temporary or permanent protection of hydroxy functions, e.g. the silyl, alkoxyalkyl, acyl or alkoxycarbonyl groups, as previously defined. The terms "hydroxyalkyl", "deuteroalkyl" and "fluoroalkyl" refer to an alkyl radical substituted by one or more hydroxy, deuterium or fluoro groups respectively.

[0028] It should be noted in this description that the term "24-homo" refers to the addition of one methylene group and the term "24-dihomo" refers to the addition of two methylene groups at the carbon 24 position in the side chain. Likewise, the term "trihomo" refers to the addition of three methylene groups. Also, the term "26,27-dimethyl" refers to the addition of a methyl group at the carbon 26 and 27 positions so that for example R^3 and R^4 are ethyl groups. Likewise, the term "26,27-diethyl" refers to the addition of an ethyl group at the 26 and 27 positions so that R^3 and R^4 are propyl groups.

[0029] In the following lists of side chain unsaturated and side chain saturated compounds, if the methyl group attached at the carbon 20 position is in its epi or unnatural configuration, the term "20(S)" or "20-epi" should be included in each of the following named compounds. Also, if the side chain contains an oxygen atom substituted at any of positions 20, 22 or 23, the term "20-oxa,""22-oxa" or "23-oxa," respectively, should be added to the named compound. The named compounds could also be of the vitamin D_2 type if desired.

[0030] Specific and preferred examples of the 2-alkylidene-18,19-dinor-vitamin D compounds of structure I when the side chain is unsaturated are:

[0031] 2-methylene-18,19-dinor-1α-hydroxy-22-dehydrovitamin D_3;

[0032] 2-methylene-18,19-dinor-25-hydroxy-22-dehydrovitamin D_3;

[0033] 2-methylene-18,19-dinor-1α,25-dihydroxy-22-dehydrovitamin D_3;

[0034] 2-methylene-18,19-dinor-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;

[0035] 2-methylene-18,19-dinor-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

[0036] 2-methylene-18,19-dinor-24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

[0037] 2-methylene-18,19-dinor-26,27-dimethyl-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;

[0038] 2-methylene-18,19-dinor-26,27-dimethyl-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

[0039] 2-methylene-18,19-dinor-26,27-dimethyl-24-trihomo-1,25 -dihydroxy-22-dehydrovitamin D_3;

[0040] 2-methylene-18,19-dinor-26,27-diethyl-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;

[0041] 2-methylene-18,19-dinor-26,27-diethyl-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

[0042] 2-methylene-18,19-dinor-26,27-diethyl-24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3;

[0043] 2-methylene-18,19-dinor-26,27-dipropyl-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;

[0044] 2-methylene-18,19-dinor-26,27-dipropyl-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3; and

[0045] 2-methylene-18,19-dinor-26,27-dipropyl-24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3.

[0046] With respect to the above unsaturated compounds, it should be noted that the double bond located between the 22 and 23 carbon atoms in the side chain may be in either the (E) or (Z) configuration. Accordingly, depending upon the configuration, the term "22,23(E)" or "22,23(Z)" could be included in each of the above named compounds. Also, it is common to designate the double bond located between the 22 and 23 carbon atoms with the designation "Δ^{22}". Thus, for example, the fourth named compound above could also be written as 2-methylene-18,19-dinor-24-homo-22,23(E)-Δ^{22}-1,25-$(OH)_2D_3$ where the double bond is the (E) configuration. Similarly, if the methyl group attached at carbon 20 is in the unnatural configuration, this compound could be written as 2-methylene-18,19-dinor-20(S)-24-homo-22,23(E)-Δ^{22}-1,25-$(OH)_2D_3$.

[0047] Specific and preferred examples of the 2-alkylidene-18,19-dinor-vitamin D compounds of structure I when the side chain is saturated are:

[0048] 2-methylene-18,19-dinor-1α-hydroxyvitamin D_3;

[0049] 2-methylene-18,19-dinor-25-hydroxyvitamin D_3;

[0050] 2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3;

[0051] 2-methylene-18,19-dinor-24-homo-1,25-dihydroxyvitamin D_3;

[0052] 2-methylene-18,19-dinor-24-dihomo-1,25-dihydroxyvitamin D_3;

[0053] 2-methylene-18,19-dinor-24-trihomo-1,25-dihydroxyvitamin D_3;

[0054] 2-methylene-18,19-dinor-26,27-dimethyl-24-homo-1,25-dihydroxyvitamin D_3;

[0055] 2-methylene-18,19-dinor-26,27-dimethyl-24-dihomo-1,25-dihydroxyvitamin D_3;

[0056] 2-methylene-18,19-dinor-26,27-dimethyl-24-trihomo-1,25-dihydroxyvitamin D_3;

[0057] 2-methylene-18,19-dinor-26,27-diethyl-24-homo-1,25-dihydroxyvitamin D_3;

[0058] 2-methylene-18,19-dinor-26,27-diethyl-24-dihomo-1,25-dihydroxyvitamin D_3;

[0059] 2-methylene-18,19-dinor-26,27-diethyl-24-trihomo-1,25-dihydroxyvitamin D_3;

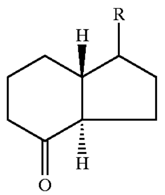
[0060] 2-methylene-18,19-dinor-26,27-dipropyl-24-homo-1,25-dihydroxyvitamin D_3;

[0061] 2-methylene-18,19-dinor-26,27-dipropyl-24-dihomo-1,25-dihydroxyvitamin D_3; and

[0062] 2-methylene-18,19-dinor-26,27-dipropyl-24-trihomo-1,25-dihydroxyvitamin D_3.

[0063] The preparation of 2-alkylidene-18,19-dinor vitamin D compounds having the structure I is based on the Wittig-Horner reaction of an 18-nor-CD-ring ketone (see (a) Baggiolini et al, J. Org. Chem., 1986, 51, 3098-3108; (b) Baggiolini et al, J. Am. Chem. Soc., 1982, 104, 2945-2948; and (c) Cohen et al, J. Org. Chem., 1979, 44, 3077-3080) and a phosphine oxide, i.e. the condensation of a bicyclic 18-nor-CD-ring type ketone II with an allylic phosphine oxide III to the corresponding 2-alkylidene-18,19-dinor vitamin D analog I followed by deprotection at C-1 and C-3 in the latter compounds:

II



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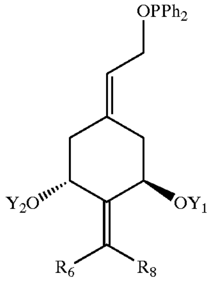
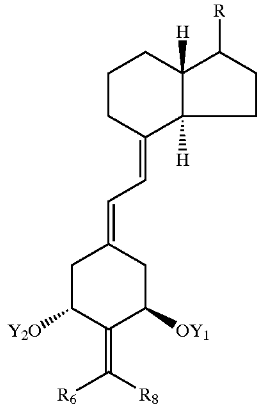
III



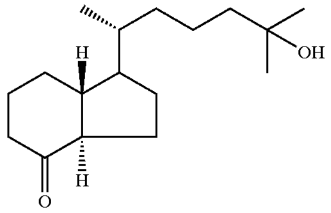
I



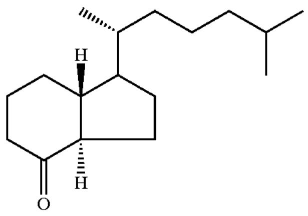
[0064] In the structures I, II and III groups R_6 and R_8, Y_1 and Y_2, and R represent groups defined above; Y_1 and Y_2 are preferably hydroxy-protecting groups such as tert-butyldimethylsilyl (TBDMS), it being also understood that any functionalities in R that might be sensitive, or that interfere with the condensation reaction, be suitably protected as is well-known in the art. The process shown above represents an application of the convergent synthesis concept, which has been applied effectively for the preparation of vitamin D compounds [e.g. Lythgoe et al., J. Chem. Soc. Perkin Trans. I, 590 (1978); Lythgoe, Chem. Soc. Rev. 9, 449 (1983); Toh et al., J. Org. Chem. 48, 1414 (1983); Baggiolini et al., J. Org. Chem. 51, 3098 (1986); Sardina et al., J. Org. Chem. 51, 1264 (1986); J. Org. Chem. 51, 1269 (1986); DeLuca et al., U.S. Pat. No. 5,086,191; DeLuca et al., U.S. Pat. No. 5,536,713].

[0065] Hydrindanones of the general structure II can be prepared starting from vitamin D_2 by the method of SCHEME 1 disclosed hereinafter. Specific important examples of such bicyclic 18-nor-CD ketones are the structures with the side chains (a), (b), (c), (d) and (e) described above, i.e. 25-hydroxy ketone (f); ketone (g); 25-hydroxy ketone (h); ketone (i) and 24-epi ketone (j). Other important 18-nor CD ketones of general structure II are the structures with the side chains (f) through (j) wherein the 20-methyl group is in its unnatural 20-epi configuration, i.e. ketones (k) through (o).

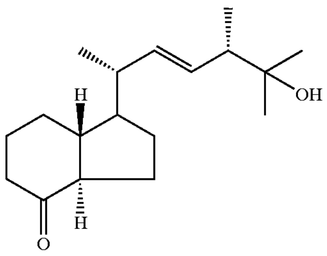
(f)



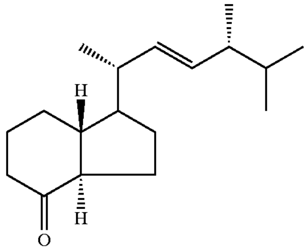
(g)



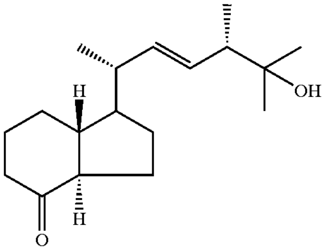
(h)



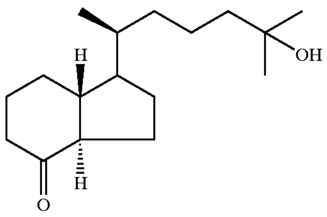
(i)



(j)



(k)



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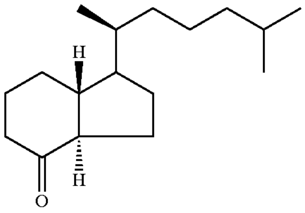
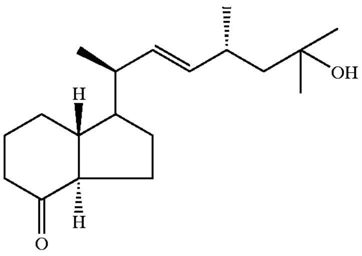
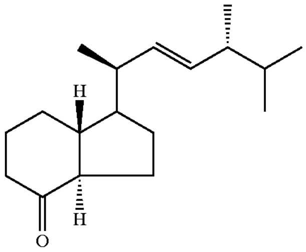
(l)



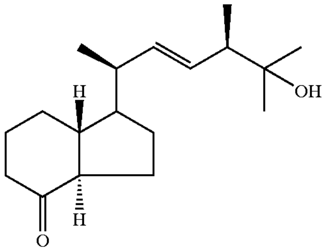
(m)



(n)



(o)



[**0066**] For the preparation of the required phosphine oxides of general structure III, a synthetic route has been developed starting from a diol, easily obtained from commercial (1R,3R,4S,5R)-(-)-quinic acid as described by Sicinski et al, J. Med. Chem., 1998, 41, 4462-4674. The overall process of transformation of the starting diol into the desired 2-alkylidene-A-ring synthon of general structure III, and more particularly, the 2-methylene-A-ring synthon 15 shown in SCHEME 1, is summarized and illustrated in U.S. Pat. No. 6,843,928, the description of which is specifically incorporated herein by reference. Thus, the starting diol will be oxidized with ruthenium tetroxide to the corresponding hydroxyketone. The latter compound will be treated with an ylide prepared from methyltriphenylphosphonium bromide and n-butyllithium. The product of the Wittig reaction will be reduced by lithium aluminum hydride to a vicinal diol, which will be cleaved by sodium periodate, and the resulting ketone will be converted to an unsaturated ester by the Peterson olefination with methyl (trimethylsilyl)acetate. The ester will then be reduced with DIBALH to an allylic alcohol which will be in situ tosylated with n-butyllithium and p-toluenesulfonyl chloride, converted into the corresponding phosphine by a reaction with diphenylphosphine lithium salt, and oxidized with hydrogen peroxide to the desired A-ring phosphine oxide 15. The Wittig-Homer coupling of the two fragments 14 and 15, to give the protected vitamin compound 16, followed by the deprotection of hydroxy groups in any known manner such as with tetrabutylammonium fluoride, will give the final analog 17.

[0067] Numerous 2-alkylidene-18,19-dinor-vitamin D compounds of the general structure I may be synthesized using the A-ring synthon III and the appropriate 18-nor-CD-ring ketone II having the desired side chain structure R. Thus, for example, Wittig-Horner coupling of the A-ring phosphine oxide 15 with n-butyllithium and any of the ketones (f), (g), (h), (i), (j), (k), (l), (m), (n) and (o) previously illustrated herein (or any other ketone with the desired side chain defined by R) may be performed as illustrated in SCHEME 1 to give the respective protected vitamin compound. This, after deprotection then affords the desired 2-methylene-18,19-dinor-vitamin D analog having the desired side chain structure R.

[0068] The C-20 epimerization may be accomplished by the analogous coupling of the phosphine oxide of structure III with the appropriate protected (20S)-CD-ring ketone of structure II which after hydrolysis of the hydroxy-protecting groups will give the desired (20S)-2-alkylidene-18,19-dinor-vitamin D analog having the desired side chain structure R.

[0069] As noted above, other 2-alkylidene-18,19-dinor-vitamin D analogs may be synthesized by the method disclosed herein. For example, 1α-hydroxy-2-methylene-18,19-dinor-vitamin D_3 can be obtained by providing the CD-ring ketone (g).

[0070] This invention is described by the following illustrative examples. In these examples specific products identified by Arabic numerals (e.g. 1, 2, 3, etc) refer to the specific structures so identified in the preceding description and in SCHEME 1.

EXAMPLE 1

[0071] Preparation of (20S)-2-methylene-1α,25-dihydroxy-18,19-dinor-vitamin D_3 (17) via condensation (SCHEME I).

[0072] Des-A,B-23,24-dinorcholane-8β,22-diol (1). A solution of vitamin D_2 (5 g, 12.7 mmol) in methanol (400 mL) and pyridine (5 mL) was cooled to −78° C. while purging with argon. The argon stream was stopped and a stream of ozone was passed until a blue color appeared. The solution was purged with oxygen until blue color disappeared and treated with $NaBH_4$ (1.2 g, 32 mmol). After 20 min. the second portion of $NaBH_4$ (1.2 g, 32 mmol) was added and reaction was allowed to warm to room temperature. The third portion of $NaBH_4$ (1.2 g, 32 mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with 70 mL of water and concentrated under vacuum. The residue was extracted with methylene chloride (3×100 mL). The organic phase was washed with 1M aqueous solution of HCl (2×100 mL), saturated aqueous solution of $NaHCO_3$ (100 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (25% ethyl acetate/hexane) to yield 1.875 g (8.84 mmol, 70% yield) of diol 1 as white crystals. $[\alpha]_D$+56.0 (c 0.95, $CHCl_3$); mp 110-111° C.; ^1H NMR (400 MHz, $CDCl_3$) δ0.96 (3H, s), 1.03 (3H, d, J=6.6 Hz), 3.38 (1H, dd, J=10.5 Hz, J=6.8 Hz), 3.64 (1H, dd, J=10.5 Hz, J=3.2 Hz), 4.09 (1H, d, J=2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 613.6, 16.6, 17.4, 22.6, 26.6, 33.5, 38.2, 40.2, 41.3, 52.3, 52.9, 67.8, 69.2; MS (EI) m/z 212 (2, M^{30}), 194 (17), 179 (18), 163 (10), 135 (19), 125 (34), 111 (100); exact mass calculated for $C_{13}H_{22}0$ ($[M-H_2O]^+$) 194.1671, found 194.1665.

[0073] Des-A,B-8β-(benzoyloxy)-23,24-dinorcholane-22-ol (2). Diol 1 (1.85 g, 8.79 mmol) was dissolved in pyridine (30 mL) and DMAP (45 mg, 0.3 mmol) was added. The solution was cooled to 0° C. then benzoyl chloride (3 mL, 3.6 g, 25 mmol) was added dropwise. The reaction mixture was kept at 5° C. for 24 h. Methylene chloride (100 mL) was added and the resulting mixture was washed with 5% aqueous solution of HCl (100 mL), saturated aqueous solution of $CuSO_4$ (2×80 mL), saturated aqueous solution of $NaHCO_3$ (80 mL) and water (100 mL). The extract was dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo afforded a crude dibenzoate.

[0074] The crude dibenzoate (5.05 g) was added at room temperature to a solution of KOH (87%, 1.5 g, 23.3 mmol) in absolute ethanol (30 mL). The resulting reaction mixture was stirred at room temperature for 3 h 20 min. Then the reaction mixture was quenched with ice and neutralized with 5% aqueous solution of HCl. The reaction mixture was extracted with methylene chloride (3×60 mL) The combined organic phases were washed with saturated aqueous solution of $NaHCO_3$ (50 mL) and dried over anhydrous $MgSO_4$. Drying agent was removed and solvent was evaporated in vacuo. Pure product was obtained by column chromatography (25% ethyl acetate/hexane) to give 2.58 g (8.16 mmol, 93% yield from diol 1) of monobenzoate 2. $[\alpha]_D$+65.2 (c 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ3.39 (1H, dd, J=10.4 Hz, J=6.8 Hz), 3.65 (1H, dd, J=10.5 Hz, J=3.2 Hz), 5.42 (1H, br d, J=22.2 Hz), 7.45 (2H, m), 7.56 (1H, m), 8.05 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ13.6, 16.6, 18.0, 22.7, 26.6, 30.5, 38.4, 39.8, 41.9, 51.4, 52.7, 67.7, 72.1, 128.3, 129.5, 130.8, 166.5; MS (EI) m/z 211 (4), 194 (52), 179 (11), 135 (41), 108 (23), 105 (100); exact mass (ESI) calculated for $C_{20}H_{28}O_3Na$ ($[M+Na]^+$) 339.1936, found 339.1941.

[0075] Des-A,B-8β-(benzoyloxy)-23,24-dinorcholane-22-al (3). Sulfur trioxide pyridine complex (7.02 g, 44.1 mmol) was added to a solution of alcohol 2 (2.32 g, 7.34 mmol) and triethylamine (5.15 mL, 3.71 g, 36.7 mmol) in anhydrous methylene chloride (30 mL) and DMSO (8 mL) at 0° C. The reaction mixture was stirred under argon for 20 min. at 0° C. and then concentrated in vacuo. The residue was purified by column chromatography (5% ethyl acetate/hexane) to give 2.05 g (6.53 mmol, 90% yield) of aldehyde 3. $[\alpha]_D$+67.4 (c 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ1.10 (3H, s), 1.15 (3H, d, J=6.8 Hz), 5.44 (1H, br d, J=2.2 Hz), 7.45 (2H, m), 7.56 (1H, m), 8.05 (2H, m), 9.60 (1H, d, J=3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ13.6, 14.1, 18.1, 23.1, 26.2, 30.7, 39.8, 42.6, 49.2, 51.2, 51.5, 128.6, 129.7, 130.9, 133.0, 205.0; MS (EI) m/z 285 (3), 216 (3), 208 (9), 180 (17), 162 (47), 147 (21), 135 (46), 122 (16), 105 (100), 95 (22), 77 (49); exact mass (ESI) calculated for $C_{19}H_{25}O_2$ ($[M-CHO]^+$) 285.1855, found 285.1848.

[0076] (20R)-Des-A,B-8β-(benzoyloxy)-23,24-dinorcholane-22-ol (4). To a solution of aldehyde 3 (2.05 g, 6.53

mmol) in methylene dichloride (25 mL), 40% aqueous solution of n-Bu$_4$NOH (8.4 mL, 12.9 mmol) was added. The resulting reaction mixture was vigorously stirred overnight. Methylene dichloride (30 mL) was then added and the mixture was washed with water (20 mL), dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5% ethyl acetate/hexane) to give 1.50 g (4.78 mmol) of the mixture of diastereoisomeric aldehydes.

[**0077**] The mixture of aldehydes was dissolved in ethanol (15 mL) and NaBH$_4$ (350 mg, 9.2 mmol) was added. The resulting mixture was stirred for 30 min. The reaction mixture was quenched with saturated aqueous solution of NH$_4$Cl (30 mL). The mixture was extracted with methylene dichloride (3×40 mL) and the combined organic phases were washed with water (30 mL), dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5% ethyl acetate/hexane) to give 870 mg (2.75 mmol, 42% yield) of 4 and 437 mg (1.38 mmol, 21% yield) of 2. $[\alpha]_D$+50.0 (c 1.10, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ0.97 (3H, d, J=6.7 Hz), 1.07 (3H, s), 3.48 (1H, dd, J=10.5 Hz, J=7.1 Hz), 3.76 (1H, dd, J=10.6 Hz, J=3.5 Hz), 5.42 (1H, s), 7.45 (2H, m), 7.55 (1H, m), 8.05 (2H, m); 13C NMR (125 MHz, CDCl$_3$) δ13.9, 16.5, 18.0, 22.5, 26.4, 30.5, 37.5, 39.3, 41.7, 51.5, 52.7, 66.9, 72.0, 128.3, 129.5, 130.8, 166.5; MS (EI) m/z 316 (16, M^{30}), 301 (5), 285 (9), 242 (11), 194 (60), 147 (71), 105 (100); exact mass (ESI) calculated for $C_{20}H_{28}O_3Na$ ([M+Na]$^+$) 339.1936, found 339.1948.

[**0078**] (20R)-Des-A,B-8β-(benzoyloxy)-23,24-dinor-22-(tosyloxy)cholane (5). To a mixture of alcohol 4 (870 mg, 2.75 mmol), triethylamine (1.5 mL, 10.8 mmol) and DMAP (20 mg) in anhydrous methylene dichloride (20 mL) tosyl chloride (710 mg, 3.73 mmol) was added at 0° C. The reaction mixture was allowed to stand at room temperature for 16 h. Then methylene dichloride (100 mL) was added and the mixture was washed with saturated aqueous solution of NaHCO$_3$ (2×50 mL), dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5% ethyl acetate/hexane) to give 1162 mg (2.47 mmol, 90% yield) of 5. $[\alpha]_D$+14.2 (c 0.95, CHCl$_3$); mp. 100-102° C.; ^{1}H NMR (500 MHz, CDCl$_3$) δ0.90 (3H, d, J=6.6 Hz), 0.98 (3H, s), 2.46 (3H, s), 3.83 (1H, dd, J=9.2 Hz, J=7.2 Hz), 4.15 (1H, dd, J=9.3 Hz, J=3.3 Hz), 7.35 (2H, d, J=8.1 Hz), 7.44 (2H, m), 7.55 (1H, m), 7.80 (2H, d, J=8.1 Hz), 8.02 (2H, m); 1^{3}C NMR (125 MHz, CDCl$_3$) δ13.9, 16.6, 17.9, 21.6, 22.3, 26.3, 30.4, 34.8, 39.1, 41.6, 71.8, 74.0, 127.9, 128.4, 129.5, 129.7, 130.7, 132.8, 133.1, 144.6, 166.7; MS (EI) m/z 365 (12), 348 (61), 193 (9), 176 (32), 161 (13), 134 (19), 105 (100), 91 (17), 77 (20); exact mass (ESI) calculated for $C_{27}H_{34}O_5SNa$ ([M+Na]$^+$) 493.2025, found 493.2032.

[**0079**] (20S)-Des-A,B-cholestan-8β-ol (7). Magnesium turnings (4.41 g, 184 mmol) were stirred with a magnetic stir bar overnight under argon. Anhydrous THF (50 mL) and 1-chloro-3-methylbutane (11 mL, 90.8 mmol) were then added. The mixture was refluxed for 6 h. The resulting solution of Grignard reagent 6 was then added via cannula to a stirred solution of 5 in anhydrous THF (15 mL) at −78° C. followed by addition of a solution of dilithium tetrachlorocuprate (620 mg, 2.73 mmol) in anhydrous THF (27 mL). The cooling bath was removed and the reaction mixture was stirred overnight. The reaction mixture was poured into a stirred mixture of ice (15 mL) and saturated aqueous solution of NH$_4$Cl (40 mL). The mixture was then extracted with ethyl acetate (3×100 mL), washed with water and dried over anhydrous Na$_2$SO$_4$. The residue was purified by column chromatography (5 to 25% ethyl acetate/hexane) to give 389 mg (1.46 mmol, 58% yield) of 7. $[\alpha]_D$+9.6 (c 1.15, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ0.82 (3H, d, J=6.6 Hz), 0.87 (6H, d, J=6.6 Hz), 0.93 (3H, s), 4.07 (1H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ13.8, 17.5, 18.5, 22.4, 22.5, 22.6, 22.7, 24.0, 27.1, 28.0, 29.7, 33.6, 34.8, 35.5, 39.4, 40.3, 41.9, 52.7, 56.3, 69.5; MS (EI) m/z 266 (45, M^{30}), 251 (19), 233 (8), 177 (9), 163 (11), 152 (20), 135 (30), 125 (37), 1 11(100); exact mass calculated for $C_{18}H_{34}O$ 266.26310, found 266.2623.

[**0080**] (20S)-Des-A,B-cholestan-8β-yl nitrite (8). A solution of 7 (185 mg, 0.69 mmol) in chloroform (5 mL) was treated with tert-butyl nitrite (1 mL) for 1 h in darkness. Benzene (10 mL) was then added and solvents were removed under reduced pressure, protecting the mixture from light. ^{1}H NMR (500 MHz, CDCl$_3$) δ0.76 (3H, s), 0.81 (3H, d, J=6.5 Hz), 0.87 (6H, d, J=6.6 Hz), 5.78 (1H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ13.1, 17.9, 18.5, 22.2, 22.6, 22.7, 23.9, 27.1, 28.0, 31.5, 34.9, 35.3, 39.3, 39.7, 41.9, 51.9, 56.0.

[**0081**] (18E)-(20S)-18-(Hydroxyimino)-des-A,B-cholestan-8β-ol (9). Crude nitrite was dissolved in anhydrous benzene (150 mL) and irradiated in an apparatus consisting of a Pyrex vessel with a watercooled immersion well and Hanovia high-pressure mercury arc lamp equipped with Pyrex filter. A slow stream of argon was passed through solution and temperature was maintained at about 10° C. A reaction progress was monitored by TLC. After 30 min. reaction was completed. Benzene was removed under reduced pressure and the residue was dissolved in 2-propanol (5 mL) and refluxed for 2 h, cooled and allowed to stand overnight to accomplish isomerisation of a nitroso compound to an oxime. The solvent was evaporated and the residue was purified on Waters silica gel Sep-Pack cartridge (25% ethyl acetate/hexane) to give 102 mg (0.35 mmol, 51% yield from 7) of the oxime 9. $[\alpha]_D$+8.2 (c 0.80, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ0.84 (3H, d, J=6.3 Hz), 0.87 (6H, d, J=6.6 Hz), 2.20 (1H, br d, J=13.1 Hz), 4.04 (1H, br d, J=2.6 Hz), 7.33 (1H, s), 10.8 (1H, br s); ^{13}C NMR (100 MHz, CDCl$_3$) δ17.5, 18.6, 21.8, 22.6, 22.7, 24.1, 27.2, 28.0, 34.3, 35.0, 35.6, 39.3, 49.5, 52.6, 56.7, 67.6, 152.2; MS (EI) m/z 295 (2, M+), 278 (28), 260 (20), 245 (8), 206 (19), 183 (38), 165 (13), 148 (15), 121 (100); exact mass calculated for $C_{18}H_{33}NO_2Na$ ([M+Na]$^+$) 318.2409, found 318.2412.

[**0082**] (20S)-8β-(Acetoxy)-des-A,B-cholestan-18-nitrile (10). A solution of 9 (100 mg, 0.34 mmol) in acetic anhydride (5 mL) was refluxed for 1.5 h. The reaction mixture was cooled, poured carefully into ice and extracted with benzene (3×40 mL). The combined organic phases were washed with saturated aqueous solution of NaHCO$_3$ (2×40 mL), water (30 mL), dried over anhydrous Na$_2$SO$_4$ and evaporated. The residue was purified on a Waters silica gel Sep-Pack cartridge (5% ethyl acetate/hexane) to give 91 mg (0.28 mmol, 84% yield) of 9. $[\alpha]_D$−26.4 (c 0.75, CHCl$_3$); IR (CHCl$_3$) 2228, 1741, 1241; ^{1}H NMR (500 MHz, CDCl$_3$) δ0.87 (6H, d, J=6.6 Hz), 0.91 (3H, d, J=6.6 Hz), 2.15 (3H, s), 2.46 (1H, br d, J=3.2 Hz), 5.20 (1H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ17.9, 18.8, 22.6, 22.7, 23.3, 23.8, 27.1, 28.0, 29.9, 35.6, 36.2, 36.3, 39.1, 45.6, 51.9, 54.1, 68.7, 121.2, 171.0; MS (EI) m/z 319 (18, M+), 304 (10), 290 (3), 277 (84), 259 (100), 244 (54), 234 (27), 216 (40), 202 (33), 188

(60), 174 (47), 147 (39), 134 (34), 121 (95); exact mass (ESI) calculated for $C_{20}H_{33}NO_2Na$ ($[M+Na]^+$) 342.2409, found 342.2413.

[0083] (20S)-Des-A,B-cholestan-18-nitrile-8β-ol (11). 10 (90 mg, 0.28 mmol) was dissolved in methanol (3 mL) and treated with 5% solution of MeONa in methanol (3 mL) for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (5 mL), water (10 mL), extracted with methylene dichloride (5×40 mL), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified on a Waters silica gel Sep-Pack cartridge (20% ethyl acetate/hexane) to give 73 mg (0.26 mmol, 94% yield) of 10. $[\alpha]_D$−6.1 (c 0.75, $CHCl_3$); IR ($CHCl_3$) 3486, 2228; ^{1}H NMR (500 MHz, $CDCl_3$) δ0.87 (6H, d, J=6.6 Hz), 0.92 (3H, d, J=6.7 Hz), 2.43 (1H, br d, J=3.1 Hz), 4.10 (1H, s); 1^{3}C NMR (125 MHz, $CDCl_3$) δ17.9, 22.6, 22.7, 22.9, 23.9, 27.1, 28.0, 32.8, 35.7, 36.2, 36.3, 44.7, 53.4, 54.2, 122.5; MS (EI) m/z 277 (28, M^+), 262 (34), 259 (18), 248 (16), 244 (24), 220 (30), 216 (18), 206 (100); exact mass calculated for $C_{18}H_{31}NO$ 277.2496, found 277.2395.

[0084] (20S)-Des-A,B-18-norcholestan-8β-ol (12). To a stirred mixture of potassium (110 mg, 2.82 mmol) in HMPA (280 μl, 1.62 mmol) and diethyl ether (700 μl) a solution of 11 (70 mg, 0.25 mmol) in tert-butyl alcohol (65 μl) and diethyl ether (250 μl) was added dropwise at 0° C. under argon. The mixture was allowed to warm up to room temperature and stirred for 5 h. Remaining potassium was removed, a few drops of 2-propanol and benzene (20 mL) were added. Organic phase was washed with water (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified on Waters silica gel Sep-Pack cartridge (10% ethyl acetate/hexane) to give 54 mg (0.21 mmol, 85% yield) of 12. $[\alpha]_D$+32.6 (c 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ0.78 (3H, d, J=6.8 Hz), 0.87 (6H, d, J=6.6 Hz), 4.06 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ14.7, 20.2, 22.7, 22.9, 24.7, 25.3, 28.0, 30.8, 33.1, 33.5, 36.3, 39.3, 39.7, 48.6, 50.3, 67.9; MS (EI) m/z 252 (6, M^+), 234 (21), 219 (23), 209 (26), 191 (8), 179 (4), 167 (13), 149 (89), 139 (47), 122 (90), 107 (35), 95 (80), 79 (87), 67 (88), 58 (100); exact mass calculated for $C_{17}H_{32}O$ 252.2453, found 252.2448.

[0085] (20S)-Des-A,B-25-hydroxy-18-norcholestane-8-one (13). To a stirred solution of $RuCl_3 \times H_2O$ (10 mg, 0.05 mmol) and $NaIO_4$ (227 mg, 1.06 mmol) in water (1 mL) a solution of 12 (74 mg, 0.29 mmol) in teterachloromethane (0.75 mL) and acetonitrile (0.75 mL) was added. The reaction mixture was vigorously stirred for 3 days. Then a few drops of 2-propanol and water (10 mL) were added. Reaction products were extracted with methylene dichloride (3×20 mL). Organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified on Waters silica gel Sep-Pack cartridge (10 to 30% ethyl acetate/hexane) to give 13 mg (0.05 mmol, 17% yield) of 13. ^{1}H NMR (400 MHz, $CDCl_3$) δ0.78 (3H, d, J=6.7 Hz), 1.22 (6H, s), 2.01 (1H, br d, J =12.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.3, 21.3, 22.2, 22.6, 27.8, 29.3, 29.7, 33.0, 36.5, 41.6, 44.1, 49.6, 51.0, 58.0, 71.0, 212.0; MS (EI) m/z 264 (3), 248 (57), 233 (19), 215 (4), 208 (15), 163 (29), 137 (100); exact mass (ESI) calculated for $C_{17}H_{30}O_2Na$ ($[M+Na]^+$) 289.2144, found 289.2136.

[0086] (20S)-25-[(Triethylsilyl)oxyl-des-A,B-18-norcholestane-8-one (14). To a stirred solution of 13 (12 mg, 45 μmol) and 2,6-lutidine (13 μl, 100 μmol) in anhydrous methylene dichloride (250 μl) triethylsilyl trifluoromethanesulfonate was added dropwise at −50° C. under argon. After 20 min. a few drops of wet methylene dichloride and water (7 mL) were added. Reaction mixture was extracted with methylene dichloride (3×7 mL). Organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified on Waters silica gel Sep-Pack cartridge (3% ethyl acetate/hexane) and on HPLC (5% ethyl acetate/hexane, 4 mL/min., Zorbax-silica 10×250mm) to give 13 mg (34 Hmol, 76% yield) of 14. ^{1}H NMR (500 MHz, $CDCl_3$) δ0.56 (6H, q, J=7.9 Hz), 0.77 (3H, d, J=6.8 Hz), 0.94 (9H, t, J=7.9 Hz), 1.19 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ6.8, 7.1, 14.3, 21.4, 22.2, 22.7, 27.8, 29.7, 29.8, 29.9, 32.9, 36.4, 41.6, 45.2, 49.6, 51.1, 58.0, 73.4, 212.1; MS (EI) m/z 365 (8), 351 (100), 322 (6), 239 (2), 231 (25), 220 (4), 205 (15), 189 (4), 173 (92); exact mass (ESI) calculated for $C_{23}H_{44}O_2SiNa$ ($[M+Na]^+$) 403.3008, found 403.2995.

[0087] (20S)-2-Methylene-1α,25-dihydroxy-18,19-dinor-vitamin D_3 (17). To a stirred solution of phosphine oxide 15 (46 mg, 79 μmol) in anhydrous THF (600 μl) a 1.5 M solution of phenyl lithium in THF (63 μl, 95 μmol) was added at −20° C. under argon. The mixture was stirred for 20 min. and then cooled to −78° C. A precooled solution of 14 (13 mg, 34 μmol) in anhydrous THF (300 μl) was added via cannula and the reaction mixture was stirred for 3 h at −78° C. After that the reaction mixture was stirred at 4° C. overnight. Then ethyl acetate was added and organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified on Waters silica gel Sep-Pack cartridge (hexane to 2% ethyl acetate/hexane) and then on HPLC (0.05% 2-propanol/hexane, 4 mL/min., Zorbax-silica 10×250 mm) to give 13.5 mg (18 μmol, 53% yield) of protected vitamin D_3 16. WV (hexane) λ_{max}=242, 251, 261 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ0.06 (3H, s), 0.11 (3H, s), 0.17 (3H, s), 0.19 (3H, s), 0.56 (6H, q, J=8.0 Hz), 0.76 (3H, d, J=6.7 Hz), 0.94 (9H, t, J=8.0 Hz), 2.18 (1H, dd, J=12.5 Hz, J=8.1 Hz), 2.86 (1H, br d, J=13.8 Hz), 4.42 (2H, m), 4.93 (1H, s), 4.96 (1H, s), 5.92 (1H, d, J=11.1 Hz), 6.19 (1H, d, J=11.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ−5.1, −4.9, −4.9, −4.8, 6.8, 7.1, 18.2, 18.2, 22.3, 23.1, 25.8, 25.8, 27.8, 29.0, 29.7, 29.8, 29.9, 31.3, 33.6, 36.5, 38.7, 45.3, 47.5, 49.0, 50.2, 52.3, 71.9, 72.3, 73.4, 106.3, 113.7, 122.4, 132.9, 143.8, 152.9; MS (EI) m/z 687 (6), 628 (2), 612 (100), 583 (6), 555 (4), 480 (29), 366 (44); exact mass calculated for $C_{40}H_{75}O_3Si_3$ ($[M\text{-}t\text{-}Bu]^+$) 687.5024, found 687.5028.

[0088] 16 (13 mg, 17 μmol) was dissolved in anhydrous THF (5 mL). Then a 1 M solution of tetrabutyl ammonium fluoride in THF (260 μl, 260 μmol) was added dropwise followed by addition of activated molecular sieves 4A (200 mg). The reaction mixture was stirred under argon for 2 h. Then solvent was removed under reduced pressure and the residue was purified on Waters silica gel Sep-Pack cartridge (40 to 50% ethyl acetate/hexane). Crude 17 was then purified on HPLC (20% 2-propanol/hexane, 4 mL/min., Zorbax-silica 10×250 mm) to give 3.8 mg (9.5 μmol, 56% yield) of 17 at R_t=5.58 min.; UV (EtOH) λ_{max}=242,250,260 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ0.77 (3H, d, J=6.6 Hz), 1.21 (6H, s), 2.58 (1H, dd, J=13.2 Hz, J=3.9 Hz), 2.81 (1H, dd, J=13.3 Hz, J=4.4 Hz), 2.87 (1H, br d, J=13.9 Hz), 4.48 (2H, m), 5.10 (1H, s), 5.11 (1H, s), 5.97 (lH, d, J=11.3 Hz), 6.35 (1H, d, J=11.3 Hz); MS (EI) m/z 402 (39, M^+), 384 (41), 366 (14), 351 (11), 299 (58), 231 (36), 142 (58), 69 (100); exact mass calculated for $C_{26}H_{42}O_3$ 402.3134, found 402.3121.

[**0089**] For treatment purposes, the novel compounds of this invention defined by formula I may be formulated for pharmaceutical applications as a solution in innocuous solvents, or as an emulsion, suspension or dispersion in suitable solvents or carriers, or as pills, tablets or capsules, together with solid carriers, according to conventional methods known in the art. Any such formulations may also contain other pharmaceutically-acceptable and non-toxic excipients such as stabilizers, anti-oxidants, binders, coloring agents or emulsifying or taste-modifying agents.

[**0090**] The compounds may be administered orally, topically, parenterally or transdermally. The compounds are advantageously administered by injection or by intravenous infusion or suitable sterile solutions, or in the form of liquid or solid doses via the alimentary canal, or in the form of creams, ointments, patches, or similar vehicles suitable for transdermal applications. Doses of from 0.01 μg to 100 μg per day of the compounds, preferably from about 0.1 μg/day to about 50 μg/day, are appropriate for treatment purposes, such doses being adjusted according to the disease to be treated, its severity and the response of the subject as is well understood in the art. Since the new compounds exhibit specificity of action, each may be suitably administered alone, or together with graded doses of another active vitamin D compound—e.g. 1α-hydroxyvitamin D_2 or D_3, or 1α,25-dihydroxyvitamin D_3—in situations where different degrees of bone mineral mobilization and calcium transport stimulation is found to be advantageous.

[**0091**] Compositions for use in the above-mentioned treatment of psoriasis and other malignancies comprise an effective amount of one or more 2-alkylidene-18,19-dinor-vitamin D compound as defined by the above formula I as the active ingredient, and a suitable carrier. An effective amount of such compounds for use in accordance with this invention is from about 0.01 μg to about 100 μg per gm of composition, preferably from about 0.1 μg/gm to about 50 μg/gm of the composition, and may be administered topically, transdermally, orally or parenterally in dosages of from about 0.01 μg/day to about 100μg/day, preferably from about 0.1 μg/day to about 50 μg/day.

[**0092**] The compounds may be formulated as creams, lotions, ointments, topical patches, pills, capsules or tablets, or in liquid form as solutions, emulsions, dispersions, or suspensions in pharmaceutically innocuous and acceptable solvent or oils, and such preparations may contain in addition other pharmaceutically innocuous or beneficial components, such as stabilizers, antioxidants, emulsifiers, coloring agents, binders or taste-modifying agents.

[**0093**] The compounds are advantageously administered in amounts sufficient to effect the differentiation of promyelocytes to normal macrophages. Dosages as described above are suitable, it being understood that the amounts given are to be adjusted in accordance with the severity of the disease, and the condition and response of the subject as is well understood in the art.

[**0094**] The formulations of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

[**0095**] Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion.

[**0096**] Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and carrier such as cocoa butter, or in the form of an enema.

[**0097**] Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

[**0098**] Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops; or as sprays.

[**0099**] For asthma treatment, inhalation of powder, self-propelling or spray formulations, dispensed with a spray can, a nebulizer or an atomizer can be used. The formulations, when dispensed, preferably have a particle size in the range of 10 to 100μ.

[**0100**] The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient as a physically and chemically stable unit dose comprising either the active ingredient as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

2-Alkylidene-18,19-Dinor Slow Release Compounds

[**0101**] Modified vitamin D compounds that exhibit a desirable and highly advantageous pattern of biological activity in vivo, namely, the more gradual onset and more prolonged duration of activity, may also be used herein.

[**0102**] Structurally, the key feature of the modified vitamin D compounds having these desirable biological attributes is that they are derivatives of 2-alkylidene-18,19-dinor-vitamin D analogs, in which a hydrolyzable group is attached to the hydroxy group at carbon 25 and, optionally, to any other of the hydroxy groups present in the molecule. Depending on various structural factors—e.g. the type, size, structural complexity—of the attached group, these derivatives hydrolyze to the active 2-alkylidene-18,19-dinor-vitamin D analog, at different rates in vivo, thus providing for the "slow release" of the biologically active vitamin D compound in the body.

[**0103**] The "slow release" in vivo activity profiles of such compounds can, of course, be further modulated by the use of mixtures of derivatives or the use of mixtures consisting of one or more vitamin D derivative together with underivatized vitamin D compounds.

[**0104**] It is important to stress that the critical structural feature of the vitamin derivatives identified above is the presence of a hydrolyzable group attached to the hydroxy group at carbon 25 of the molecule. The presence of a hydrolyzable group at that position imparts on the resulting derivatives the desirable "slow-release" biological activity profile mentioned above. Other hydroxy functions occurring in the molecule (e.g. hydroxy functions at carbons 1 or 3) may be present as free hydroxy groups, or one or more of them may also be derivatised with a hydrolyzable group.

[**0105**] The "hydrolyzable group" present in the above-mentioned derivatives is preferably an acyl group, i.e. a group of the type Q^1CO—, where Q^1 represents hydrogen or a hydrocarbon radical of from 1 to 18 carbons that may be straight chain, cyclic, branched, saturated or unsaturated. Thus, for example, the hydrocarbon radical may be a straight chain or branched alkyl group, or a straight chain or branched alkenoyl group with one or more double bonds, or it may be an optionally substituted cycloalkyl or cycloalkenyl group, or an aromatic group, such as substituted or unsubstituted phenyl, benzyl or naphthyl. Especially preferred acyl groups are alkanoyl or alkenoyl groups, of which some typical examples are formyl, acetyl, propanoyl, hexanoyl, isobutyryl, 2-butenoyl, palmitoyl or oleoyl. Another suitable type of hydrolyzable group is the hydrocarbyloxycarbonyl group, i.e. a group of the type Q^2—O—COp**13** , where Q^2 is a C_1 to C_{18} hydrocarbon radical as defined above. Exemplary of such hydrocarbon radicals are methyl, ethyl, propyl, and higher straight chain or branched alkyl and alkenoyl radicals, as well as aromatic hydrocarbon radicals such as phenyl or benzoyl.

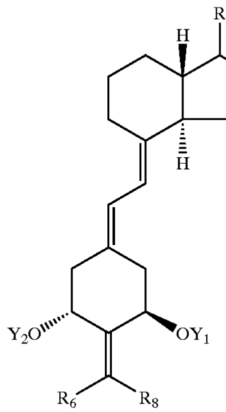
[**0106**] These modified vitamin D compounds are hydrolyzable in vivo to the active analog over a period of time following administration, and as a consequence regulate the in vivo availability of the active analog, thereby also modulating their activity profile in vivo. The term "activity profile" refers to the biological response over time of vitamin D compounds. Individual modified compounds, or mixtures of such compounds, can be administered to "fine tune" a desired time course of response.

[**0107**] As used herein the term "modified vitamin D compound" encompasses any vitamin D compound in which one or more of the hydroxy functions present in such a compound are modified by derivatization with a hydrolyzable group. A "hydrolyzable group" is a hydroxy-modifying group that can be hydrolyzed in vivo, so as to regenerate the free hydroxy functions.

[**0108**] In the context of this disclosure, the term hydrolyzable group preferably includes acyl and hydrocarbyloxycarbonyl groups, i.e. groups of the type Q^1CO— and Q^2—O—CO, respectively, where Q^1 and Q^2 have the meaning defining earlier.

[**0109**] Structurally, the modified vitamin D compounds encompassed may be represented by the formula I shown below:

I



[**0110**] where Y_1, Y_2, and R are as previously defined herein with respect to formula I with the exception that R^5 in the side chain is —OY_3 and Y_3 is an acyl group or a hydrocarbyloxycarbonyl group, as previously defined herein.

[**0111**] Some specific examples of such modified vitamin D compounds include 2-methylene-18,19-dinor derivatives such as:

[**0112**] 2-methylene-18,19-dinor-1α,25(OH)$_2$-D$_3$-1,3,25-Triacetate where Y_1=Y_2=Y_3 and is CH_3CO;

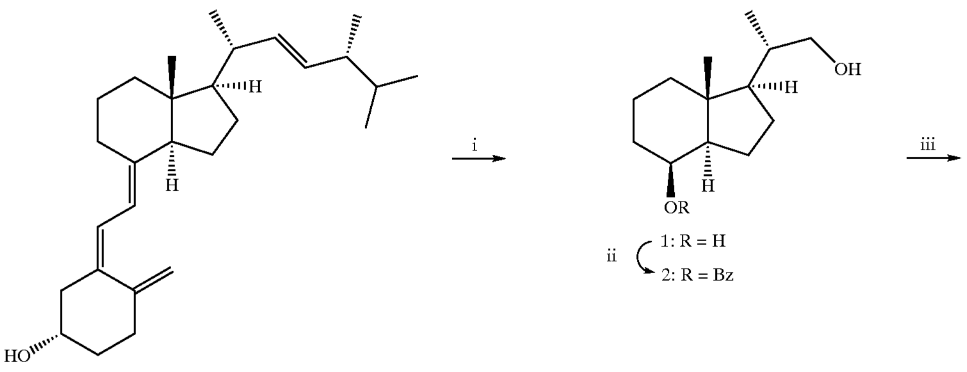
[**0113**] 2-methylene-18,19-dinor-1α,25(OH)$_2$-D$_3$-1,3,25-Trihexanoate where Y_1=Y_2=Y_3 and is $CH_3(CH_2)_4CO$;

[**0114**] 2-methylene-18,19-dinor-1α,25(OH)$_2$-D$_3$-1,3,25-Trinonanoate where Y_1=Y_2=Y_3 and is $CH_3(CH_2)_7CO$;

[**0115**] 2-methylene-18,19-dinor-1α,25(OH)$_2$-D$_3$-25-Acetate where Y_1=Y_2 and is H and Y_3 is CH_3CO.

[**0116**] These compounds can be prepared by known methods. See for example U.S. Pat. No. 5,843,927.

Scheme 1



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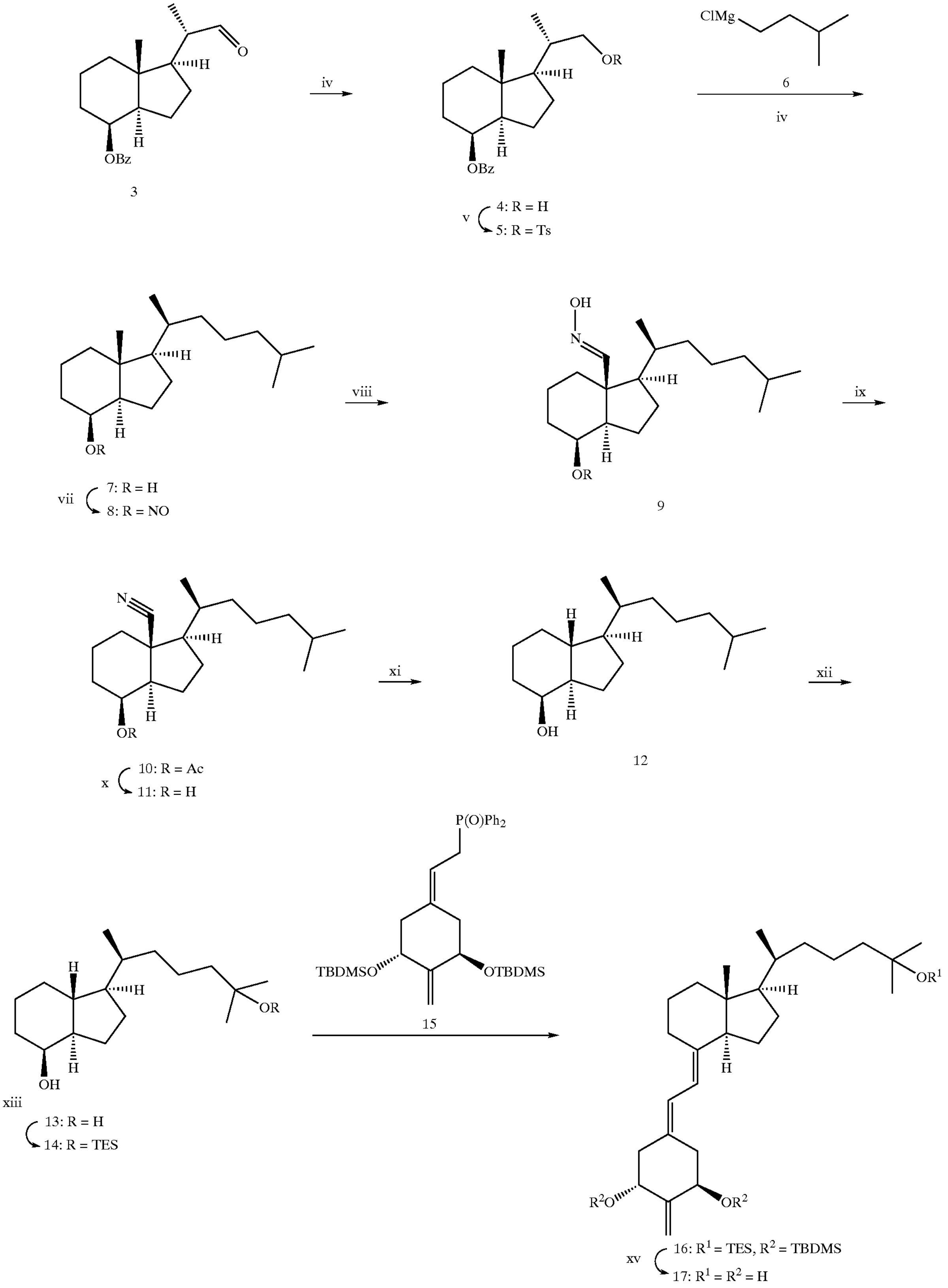
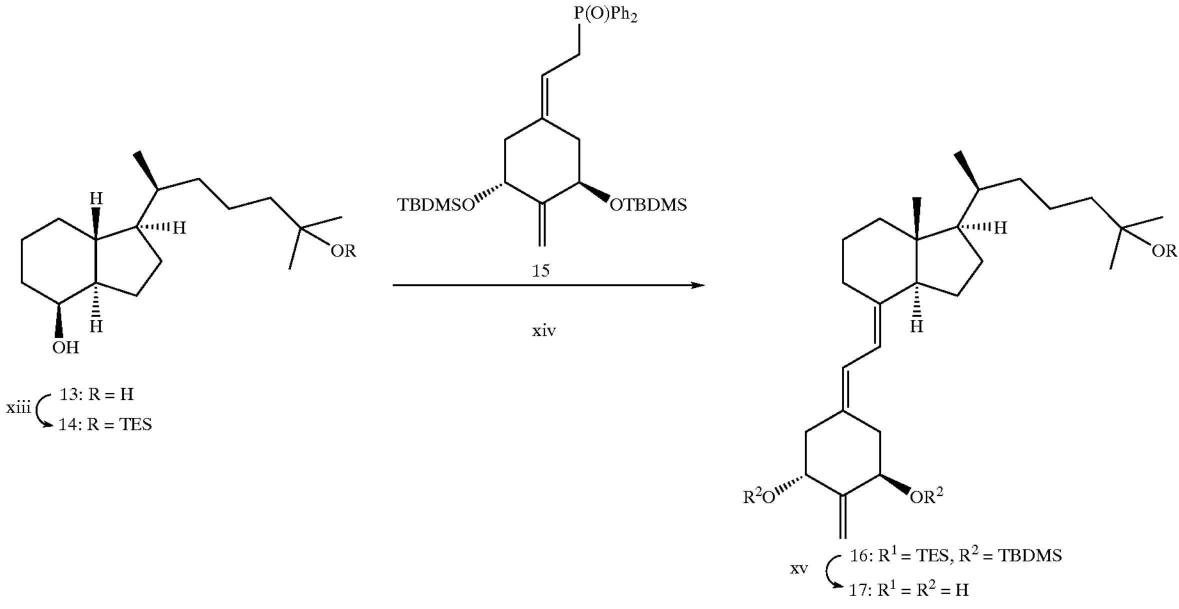

O
H
OBz
3
iv
OR
4: R = H
5: R = Ts
v
ClMg
6
iv
OR
7: R = H
8: R = NO
vii
viii
OH
N
9
ix
N
OR
10: R = Ac
11: R = H
x
xi
OH
12
xii
P(O)Ph2
TBDMSO
OTBDMS
15
OR
13: R = H
14: R = TES
xiii
OR1
R2O
OR2
16: R1 = TES, R2 = TBDMS
17: R1 = R2 = H
xv

-continued



13: R = H
14: R = TES

16: R^1 = TES, R^2 = TBDMS
17: R^1 = R^2 = H

(i) O_3, MeOH, py; $NaBH_4$, 70%.
(ii) BzCl, DMAP, py; KOH/EtOH, 93%.
(iii) SO_3/py, DMSO, Et_3N, CH_2Cl_2, 90%.
(iv) 40% aq. n-Bu_4NOH, CH_2Cl_2; $NaBH_4$, EtOH, 42%.
(v) TsCl, Et_3N, DMAP, CH_2Cl_2, 90%.
(vi) 6, Li_2CuCl_4, THF, 58%.
(vii) t-BuONO, $CHCl_3$.
(viii) hv, C_6H_6; i-PrOH, 51% (from 7).
(ix) Ac_2O, 94%.
(x) MeONa/MeOH, 91%.
(xi) K, HMPA, t-BuOH, 78%.
(xii) $RuCl_3$•H_2O, $NaIO_4$, CCl_4, CH_3CN, H_2O, 17%.
(xiii) TESOTf, 2,6-lutidine, CH_2Cl_2, 83%.
(xiv) 15, PhLi, THF, 53%.
(xv) TBAF, molecular sieves 4A, THF, 56%.

Biological Activity of 2-Alkylidene-18,19-Dinor-Vitamin D Compounds

[0117] **FIG. 1**—Competitive VDR Binding

[0118] Competitive binding of the analogs to the porcine intestinal receptor was carried out by the method described by Dame et al (Biochemistry 25, 4523-4534, 1986).

[0119] Test Material

[0120] Protein Source

[0121] Full-length recombinant rat receptor was expressed in *E. coli* BL21 (DE3) Codon Plus RIL cells and purified using two different column chromatography systems. The first system was a nickel affinity resin that utilized the C-terminal histidine tag on this protein. The protein that was eluted from this resin was further purified using ion exchange chromatography (S-Sepharose Fast Flow). Aliquots of the purified protein were quick frozen in liquid nitrogen and stored at −80° C. until use. For use, the protein was diluted in TEDK50 (50 mM Tris, 1.5 mM EDTA, pH7.4, 5 mM DTT, 150 mM KCl) with 0.1% Chaps detergent so that no more than 20% of the added radiolabeled ligand was bound to the receptor.

[0122] Study Drugs

[0123] Unlabeled ligands were dissolved in ethanol and the concentrations determined using UV spectrophotometry. Serial dilutions were prepared so that a range of unlabeled ligands could be added to the protein without changing the final concentration of ethanol (<10%) present in the assay mixture. Radiolabeled ligand (3H-1,25$(OH)_2D_3$) was added in ethanol at a final concentration of 1 nM.

[0124] Assay Conditions

[0125] Radiolabeled and unlabeled ligands were added to 100 mcl of the diluted protein, mixed and incubated overnight on ice to reach binding equilibrium. The following day, 100 mcl of hydroxylapatite slurry (50%) was added to each tube and mixed at 10-minute intervals for 30 minutes. The hydroxylapaptite was pelleted by centrifugation and then washed three times with Tris-EDTA buffer (50 mM Tris, 1.5 mM EDTA, pH 7.4) containing 0.5% Titron X-100. After the final wash, the pellets were transferred to scintillation vials containing 4 ml of Biosafe II scintillation cocktail, mixed and placed in a scintillation counter. Total binding was determined from the tubes containing only radiolabeled ligand. The percentage of competition was calculated by subtracting the number of dpm remaining in the hydroxylapatite pellet from the total number of dpm bound, dividing by the total number of dpm bound and multiplying by one hundred. Duplicate tubes were prepared and analyzed for each test concentration.

[0126] **FIG. 2**—HL-60 Cell Differentiation

[0127] The differentiation of HL-60 promyelocytic into monocytes was determined as described by Ostrem et al (J. Biol. Chem. 262, 14164-14171, 1987).

[0128] Test Material

[0129] Study Drugs

[0130] The study drugs were dissolved in ethanol and the concentrations determined using UV spectrophotometry (2MD: molar extinction coefficient=42,000 and Imax =252nm; 1,25$(OH)_2D_3$: molar extinction =18,200 and Imax=265 nm). Serial dilutions were prepared so that a range of drug concentrations could be tested without changing the final concentration of ethanol (<0.2%) present in the cell cultures.

[0131] Cells

[0132] Human promyelocytic leukemia (HL60) cells were grown in RPMI-1640 medium containing 10% fetal bovine serum. The cells were incubated at 37° C. in the presence of 5% CO_2.

[0133] Assay Conditions

[0134] HL60 cells were plated at 1.2×105 cells/ml. Eighteen hours after plating, the cells were administered the drug in ethanol. Four days post-dose, the cells were harvested and a nitro blue tetrazolium reduction assay was performed (Collins et al., 1979; J. Exp. Med. 149:969-974, Appendix A). The percentage of differentiated cells was determined by counting a total of 200 cells and recording the number that contained intracellular black-blue formazan deposits. Verification of differentiation to monocytic cells was determined by measuring phagocytic activity (data not shown). All drug concentrations were tested in duplicate.

[0135] **FIG. 3**—Transcription Activation

[0136] Transcriptional activity was measured in ROS 17/2.8 (bone) cells that were stably transfected with a 24-hydroxylase (24OHase) gene promoter upstream of a luciferase reporter gene (Arbour et al., 1998). Cells were given a range of doses. Sixteen hours after dosing the cells were harvested and luciferase activities were measured using a luminometer.

[0137] "RLU" in **FIG. 3** refers to relative luciferase units.

[0138] **FIG. 4**—Intestinal Calcium Transport

[0139] Weanling, male Sprague-Dawley rats were purchased from Harlan. Upon receipt, the animals were identified by individual tail marks and fed a calcium containing (0.47%) diet (Suda et al., Purified Rodent Diet-Diet 11; Appendix A) for one week before switching to the same diet devoid of calcium (0.02%). Water and a purified rodent diet (Diet 11; Appendix A) containing either 0.47% or 0.02% calcium and 0.3% phosphorus were provided ad libitum. Animals were fed the purified diet containing 0.47% calcium for the first week and then the 0.02% calcium containing diet for the next three weeks of the study. The rats were then fed 0.47% calcium containing diet for one week before switching back to 0.02% calcium containing diet for the remainder of the study. During the second week back on 0.02% calcium containing diet, dose administration began. All doses were administered intraperitoneally in 100 microliters of propylene glycol. Four consecutive doses were given approximately 24 hours apart. Twenty-four hours after the last dose, blood was collected from the tail artery of each experimental animal. The blood was allowed to coagulate at room temperature and then centrifuged at 3000×g for 15 minutes. The serum was transferred to a polypropylene tube and stored frozen at −20° C. The level of calcium was determined by diluting the serum into 0.1% lanthum chloride and measuring the absorbance on an atomic absorption spectrophotometer (Perkin Elmer Model 3110, Shelton, Conn.). Twenty-four hours after the last dose, intestinal calcium transport was assessed ex vivo using the everted gut sac technique.

[0140] **FIGS. 5 and 6**—Bone Calcium Mobilization

[0141] Weanling, male Sprague-Dawley rats were purchased from Harlan. Upon receipt, the animals were identified by individual tail marks and fed a calcium containing (0.47%) diet (Suda et al., Purified Rodent Diet-Diet 11; Appendix A) for one week before switching to the same diet devoid of calcium (0.02%). Water and a purified rodent diet (Diet 11; Appendix A) containing either 0.47% or 0.02% calcium and 0.3% phosphorus were provided ad libitum. Animals were fed the purified diet containing 0.47% calcium for the first week and then the 0.02% calcium containing diet for the next three weeks of the study. The rats were then fed 0.47% calcium containing diet for one week before switching back to 0.02% calcium containing diet for the remainder of the study. During the second week back on 0.02% calcium containing diet, the animals were tail-bled (baseline serum calcium) and then dose administration was initiated. All doses were administered intraperitoneally in 100 microliters of propylene glycol. Four consecutive doses were given approximately 24 hours apart. Twenty-four hours after the last dose, blood was collected from the tail artery of each experimental animal. The blood was allowed to coagulate at room temperature and then centrifuged at 3000×g for 15 minutes. The serum was transferred to a polypropylene tube and stored frozen at −20° C. The level of calcium was determined by diluting the serum into 0.1% lanthum chloride and measuring the absorbance on an atomic absorption spectrophotometer (Perkin Elmer Model 3110, Shelton, Conn.).

Interpretation of Biological Data

[0142] **FIG. 1** illustrates the relative activity of (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (also herein referred to as "DP035"), (20S)-2-methylene-19-nor-1α,25-dihydroxyvitamin D_3, (also herein referred to as "2MD") and 1α,25-dihydroxyvitamin D_3 (also herein referred to as "C001") in binding to the 1α,25-dihydroxyvitamin D pig intestinal nuclear receptor. **FIG. 1** shows that (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 is very active in binding to the 1α,25-hydroxyvitamin D_3 receptor from porcine intestinal nuclei.

[0143] The 2-alkylidene-18,19-dinor compounds of this invention exhibit a pattern of biological activity having high potency in promoting the differentiation of malignant cells, relatively high intestinal calcium transport activity and a relatively low ability to mobilize calcium from bone. This is illustrated by the biological assay results obtained for (20S)-2-methylene-18,19-dinor-1α,25-dihydroxy-vitamin D_3 which is summarized in **FIGS. 2 through 6**. **FIG. 2** shows a comparison of the activity of the known active metabolite 1α,25-dihydroxyvitamin D_3 (C001) as well as analog 2MD and the presently claimed (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DP035) in inducing the differentiation of human leukemia cells (HL-60 cells) in culture to monocytes. Differentiation activity was assessed by a standard differentiation assay, abbreviated as NBT reduction (nitroblue tetrazolium reduction). The assay was conducted according to known procedures, as given, for example, by DeLuca et al U.S. Pat. No. 4,717,721 and Ostrem et al, J. Biol. Chem. 262, 14164, 1987. For the assay, the differentiation activity of the test compounds is expressed in terms of the percent of HL-60 cells having differentiated to normal cells in response to a given concentration of test compound.

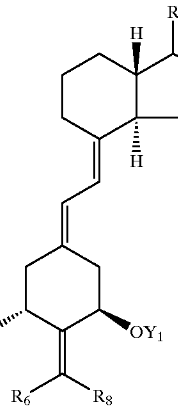
[0144] The results summarized in **FIG. 2** clearly show that the analog, (20 S)-2-methylene-1α,25-dihydroxy-18,19-dinor-vitamin D_3 (DP035) is more potent than 1α,25-dihydroxyvitamin D_3 (C001) in promoting the differentiation of leukemia cells. Thus, in the NBT assay close to 90% of the cells are induced to differentiate by 1α,25-dihydroxyvitamin D_3 (C001) at a concentration of 1×10^{-7}M, and the same degree of differentiation is achieved by the (20S)-2-methylene-18,19-dinor analog (DP035) at 1×10^{-7}M.

[0145] **FIG. 3** illustrates that (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DP035) has higher transcriptional activity than 1α,25-dihydroxyvitamin D_3 in bone cells. This result, together with the cell differentiation activity of **FIG. 2**, suggests that DP035 will be very effective in psoriasis because it has direct cellular activity in causing cell differentiation and in suppressing cell growth. These data also indicate that DP035 may have significant activity as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer.

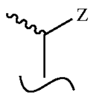
[0146] **FIGS. 4 through 6** show a comparison of the calcemic activity of the known active metabolite 1α,25-dihydroxyvitamin D_3 (C001), and the 19-nor analog 2MD and the presently claimed (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DP035). **FIG. 4** shows that (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DP035) is as active as 1α,25-dihydroxyvitamin D_3 (C001) in intestinal calcium transport activity. Also, **FIGS. 5 and 6** show that although (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DP035) has some ability to mobilize calcium from bone, it is clearly not as active in this regard as 1α,25-dihydroxyvitamin D_3 (C001). Thus, in summary, the (20S)-2-methylene-18,19-dinor analog (DP035) shows a selective activity profile combining high potency in inducing the differentiation of malignant cells, relatively high intestinal calcium transport activity and relatively low bone calcium mobilization activity.

We claim:

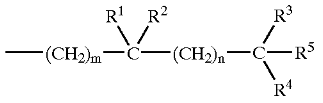
1. A compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R_6 and R_8, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group —$(CH_2)_x$— where x is an integer from 2 to 5, and where the group R is represented by the structure:



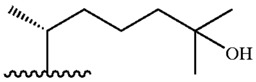
where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH_2OY, —C≡CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



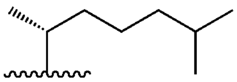
$$-(CH_2)_m-\overset{R^1\ R^2}{\overset{\diagdown\,\diagup}{C}}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group —$(CH_2)_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —$(CH_2)_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —CH(CH_3)—, —(CH_2)$_m$—, —(CH_2)$_n$—, or —CR_1R_2)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

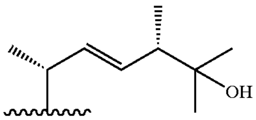
2. The compound of claim 1 where R is a side chain of the formula



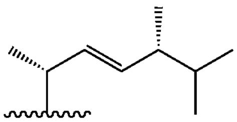
3. The compound of claim 1 where R is a side chain of the formula



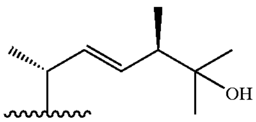
4. The compound of claim 1 where R is a side chain of the formula



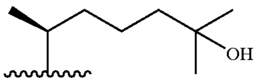
5. The compound of claim 1 where R is a side chain of the formula



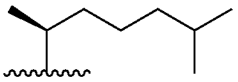
6. The compound of claim 1 where R is a side chain of the formula



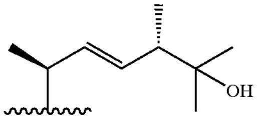
7. The compound of claim 1 where R is a side chain of the formula



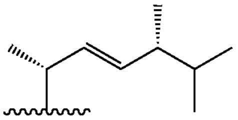
8. The compound of claim 1 where R is a side chain of the formula



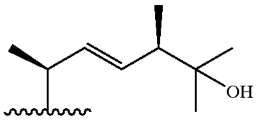
9. The compound of claim 1 where R is a side chain of the formula



10. The compound of claim 1 where R is a side chain of the formula



11. The compound of claim 1 where R is a side chain of the formula



12. (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3.

13. A pharmaceutical composition containing an effective amount of at least one compound as claimed in claim 1 together with a pharmaceutically acceptable excipient.

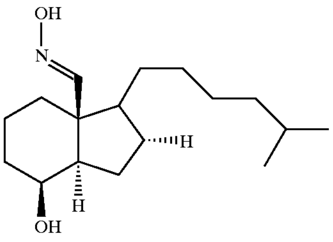
14. The pharmaceutical composition of claim 13 wherein said effective amount comprises from about 0.01 g to about 100 μg per gram of composition.

15. The pharmaceutical composition of claim 13 wherein said effective amount comprises from about 0.1 μg to about 50 μg per gram of composition.

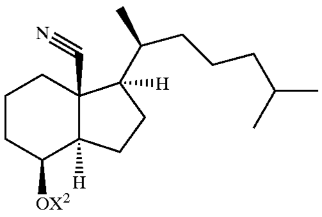
16. The pharmaceutical composition of claim 13 containing (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 in an amount from about 0.01 μg to about 100 μg.

17. The pharmaceutical composition of claim 13 containing (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 in an amount from about 0.1 μg to about 50 μg.

18. A compound having the formula:

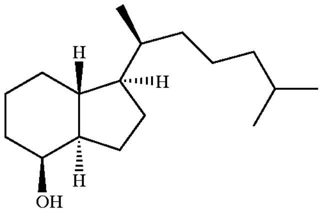


19. A compound having the formula:

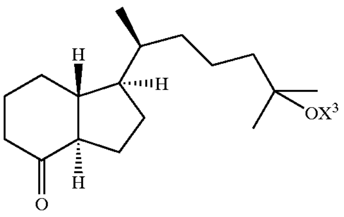


where X^2 is —H or a hydroxy protecting group.

20. A compound having the formula:

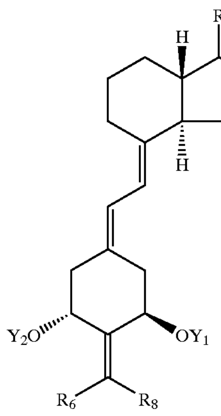


21. A compound having the formula:

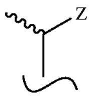


where X^3 is —H or a hydroxy protecting group.

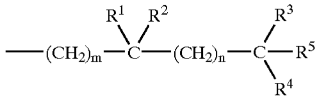
22. A method of treating metabolic bone disease where it is desired to maintain or increase bone mass comprising administering to a patient with said disease an effective amount of a compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R_6 and R_8, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group $-(CH_2)_x-$ where x is an integer from 2 to 5, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, $-CH_2OY$, —C'CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $-COR^5$ and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ R^2}{\overset{\diagdown\ \diagup}{C}}-(CH_2)_n-\underset{\diagdown\atop R^4}{\overset{R^3\atop\diagup}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group $-(CH_2)_p-$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $-(CH_2)_q-$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —$CH(CH_3)$—, —$(CH_2)_m$—, —$(CH_2)_n$— or —CR_1R_2)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

23. The method of claim 22 where the disease is senile osteoporosis.

24. The method of claim 22 where the disease is post-menopausal osteoporosis.

25. The method of claim 22 where the disease is steroid-induced osteoporosis.

26. The method of claim 22 where the disease is low bone turnover osteoporosis.

27. The method of claim 22 where the disease is osteomalacia.

28. The method of claim 22 where the disease is renal osteodystrophy.

29. The method of claim 22 wherein the compound is administered orally.

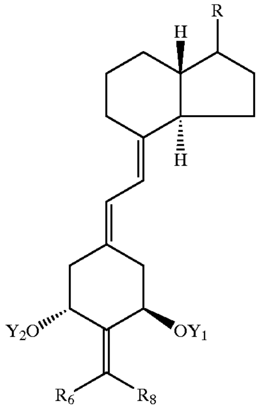
30. The method of claim 22 wherein the compound is administered parenterally.

31. The method of claim 22 wherein the compound is administered transdermally.

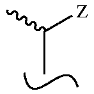
32. The method of claim 22 wherein the compound is administered in a dosage of from 0.01 μg to 100 μg per day.

33. The method of claim 22 wherein the compound is (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3.

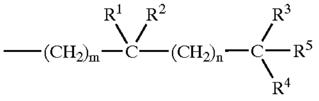
34. A method of treating psoriasis comprising administering to a patient with psoriasis an effective amount of a compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R_6 and R_8, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group —$(CH_2)_x$— where x is an integer from 2 to 5, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH_2OY, —C'CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, ═CR^2R^3, or the group —$(CH_2)_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —$(CH_2)_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —$CH(CH_3)$—, —$(CH_2)_m$—, —$(CH_2)_n$— or (CR_1R_2)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

35. The method of claim 34 wherein the compound is administered orally.

36. The method of claim 34 wherein the compound is administered parenterally.

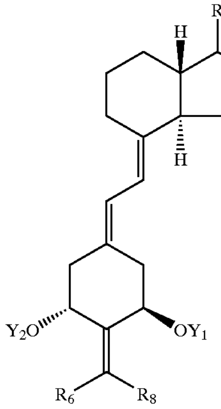
37. The method of claim 34 wherein the compound is administered transdermally.

38. The method of claim 34 wherein the compound is administered topically.

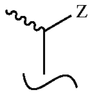
39. The method of claim 34 wherein the compound is (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3.

40. The method of claim 34 wherein said effective amount comprises about 0.01 μg/day to about 100 μg/day of said compound.

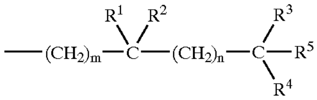
41. A method of treating leukemia, colon cancer, breast cancer, skin cancer or prostate cancer comprising administering to a patient an effective amount of a compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R_6 and R_8, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group —$(CH_2)_x$— where x is an integer from 2 to 5, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH_2OY, —C'CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$—(CH_2)_m—\overset{R^1\ R^2}{C}—(CH_2)_n—\underset{R^4}{\overset{R^3}{C}}—R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group —$(CH_2)_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —$(CH_2)_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —$CH(CH_3)$—, —$(CH_2)_m$—, —$(CH_2)_n$— or (CR_1R_2)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

42. The method of claim 41 wherein the compound is administered orally.

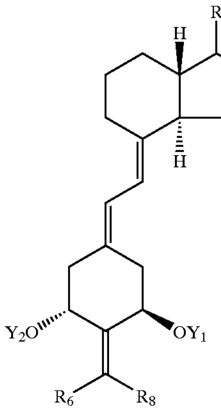
43. The method of claim 41 wherein the compound is administered parenterally.

44. The method of claim 41 wherein the compound is administered transdermally.

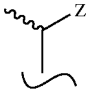
45. The method of claim 41 wherein the compound is administered in a dosage of from about 0.01 μg/day to about 100 μg/day.

46. The method of claim 41 wherein the compound is (20S)-2-methylene-19-dinor-1α,25-dihydroxyvitamin D_3.

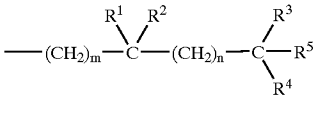
47. A method of increasing the strength of a bone comprising administering to a patient in need of such treatment an effective amount of a compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R_6 and R_8, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group —$(CH_2)_x$— where X is an integer from 2 to 5, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH_2OY, —C'CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y isselected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group —$(CH_2)_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —$(CH_2)_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —$CH(CH_3)$—, —$(CH_2)_m$—, —$(CH_2)_n$— or (CR_1R_2)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

48. The method of claim 47 wherein the bone strength is cortical strength.

49. The method of claim 47 wherein the bone strength is trabecular strength.

50. The method of claim 47 wherein the compound is administered orally.

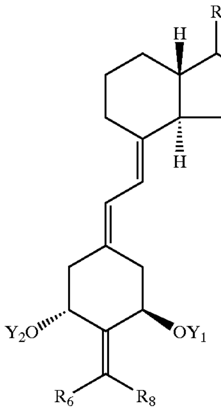
51. The method of claim 47 wherein the compound is administered parenterally.

52. The method of claim 47 wherein the compound is administered transdermally.

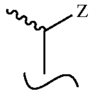
53. The method of claim 47 wherein the compound is administered in a dosage of from 0.01 μg to 100 μg per day.

54. The method of claim 47 wherein the compound is (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3.

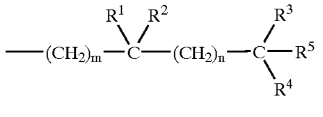
55. A method of treating an autoimmune disease comprising administering to a patient with said disease an effective amount of a compound having the formula



where Y_1 and Y_2 which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R_6 and R_8, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group —$(CH_2)_x$— where x is an integer from 2 to 5, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH_2OY, —C'CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group $-(CH_2)_p-$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $-(CH_2)_q-$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $-CH(CH_3)-$, $-(CH_2)_m-$, $-(CH_2)_n-$, or $-CR_1R_2)-$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

56. The method of claim 55 where the disease is multiple sclerosis.

57. The method of claim 55 where the disease is diabetes mellitus.

58. The method of claim 55 where the disease is lupus.

59. The method of claim 55 wherein the compound is administered orally.

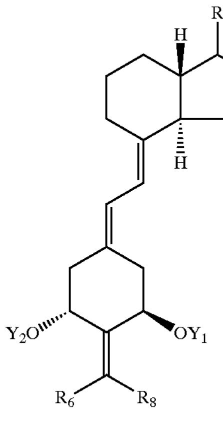
60. The method of claim 55 wherein the compound is administered parenterally.

61. Them method of claim 55 wherein the compound is administered transdermally.

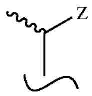
62. The method of claim 55 wherein the compound is administered in a dosage of from about 0.01 μg/day to about 100 μg/day.

63. The method of claim 55 wherein the compound is (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3.

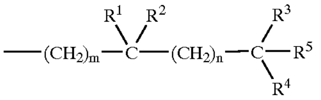
64. A method of treating an inflammatory bowel disease comprising administering to a patient with said disease an effective amount of a compound having the formula



where Y_1 and Y_2 which the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R_6 and R_8, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group $-(CH_2)_x-$ where x is an integer from 2 to 5, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, $-CH_2OY$, —C'CY and —CH═CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $-COR^5$ and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group $-(CH_2)_p-$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $-(CH_2)_q-$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $-CH(CH_3)-$, $-(CH_2)_m-$, $-(CH_2)_n-$, or $-CR_1R_2)-$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

65. The method of claim 64 wherein the disease is Crohn's disease.

66. The method of claim 64 wherein the disease is ulcerative colitis.

67. The method of claim 64 wherein the compound is administered orally.

68. The method of claim 64 wherein the compound is administered parenterally.

69. The method of claim 64 wherein the compound is administered transdermally.

70. The method of claim 64 wherein the compound is administered in a dosage of from about 0.01 μg/day to about 100 μg/day.

71. The method of claim 64 wherein the compound is (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3.

* * * * *

Exhibit I

US007241752B2

(12) United States Patent

DeLuca et al.

(10) **Patent No.: US 7,241,752 B2**

(45) **Date of Patent: Jul. 10, 2007**

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(54) **17,20(E)-DEHYDRO VITAMIN D ANALOGS AND THEIR USES**

(75) Inventors: **Hector F. DeLuca**, Deerfield, WI (US); **Bulli Padmaja Tadi**, Madison, WI (US); **Lori A. Plum**, Arena, WI (US); **Margaret Clagett-Dame**, Deerfield, WI (US)

(73) Assignee: **Wisconsin Alumni Research Foundation**, Madison, WI (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **11/283,291**

(22) Filed: **Nov. 18, 2005**

(65) **Prior Publication Data**

US 2006/0111330 A1 May 25, 2006

Related U.S. Application Data

(60) Provisional application No. 60/630,007, filed on Nov. 22, 2004.

(51) **Int. Cl.**

A61K 31/59 (2006.01)

C07C 401/00 (2006.01)

(52) **U.S. Cl.** **514/167**; 552/653

(58) **Field of Classification Search** 514/167; 552/653

See application file for complete search history.

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2004/0220418	A1 *	11/2004	DeLuca et al.	552/653

* cited by examiner

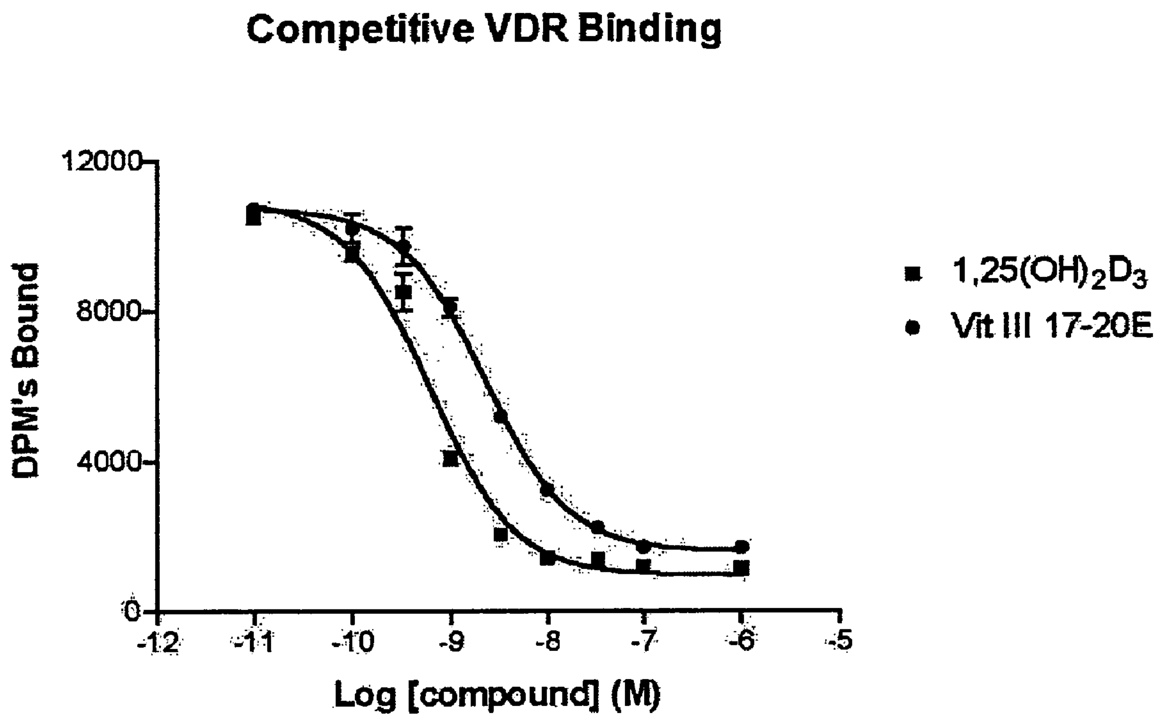
Primary Examiner—Sabiha N. Qazi

(74) *Attorney, Agent, or Firm*—Andrus, Sceales, Starke & Sawall, LLP

(57) **ABSTRACT**

This invention discloses 17,20(E)-dehydro vitamin D analogs, and specifically 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 and pharmaceutical uses therefor. This compound exhibits pronounced activity in arresting the proliferation of undifferentiated cells and inducing their differentiation to the monocyte thus evidencing use as an anti-cancer agent and for the treatment of skin diseases such as psoriasis as well as skin conditions such as wrinkles, slack skin, dry skin and insufficient sebum secretion. This compound also has little, if any, calcemic activity and therefore may be used to treat autoimmune disorders and inflammatory diseases in humans as well as renal osteodystrophy and obesity.

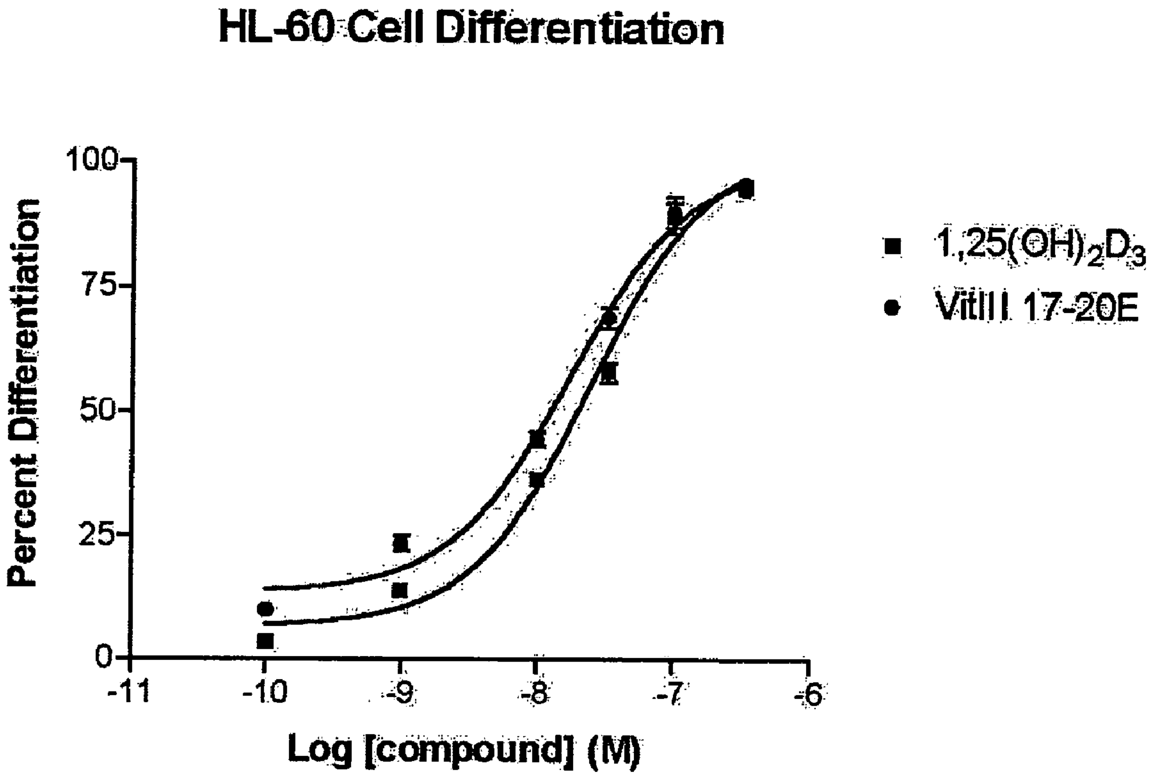
82 Claims, 5 Drawing Sheets



K_i: $1,25(OH)_2D_3 = 1.1 \times 10^{-10}$ M

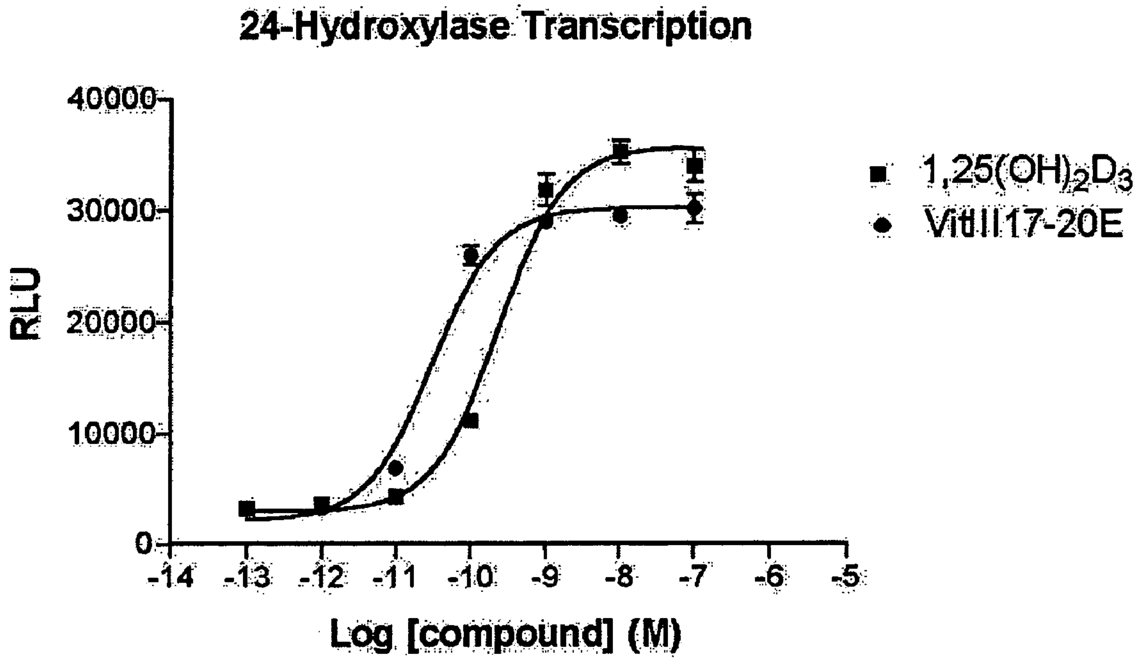
Vit-III 17-20E = 3.8×10^{-10} M

Figure 1



EC$_{50}$: 1,25(OH)$_2$D$_3$ = 2.5 x 10^{-8} M
Vit III 17-20E = 1.7 x 10^{-8} M

Figure 2



EC$_{50}$: 1,25(OH)$_2$D$_3$ = 2.3×10^{-10} M

Vit-III 17-20E = 3.1×10^{-11} M

Figure 3

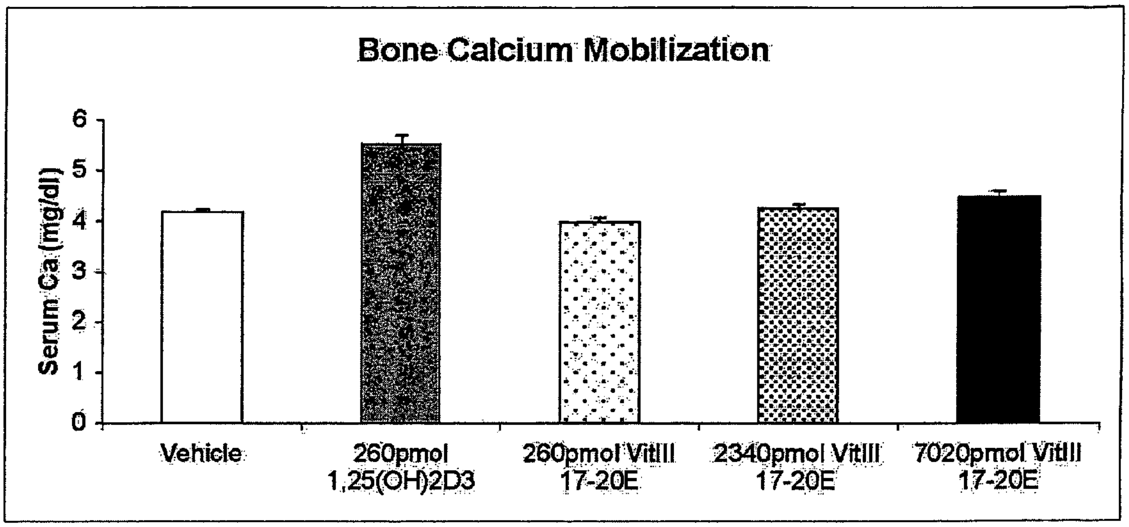

Bone Calcium Mobilization
Serum Ca (mg/dl)
0
1
2
3
4
5
6
Vehicle
260pmol 1,25(OH)2D3
260pmol VitIII 17-20E
2340pmol VitIII 17-20E
7020pmol VitIII 17-20E

Figure 4

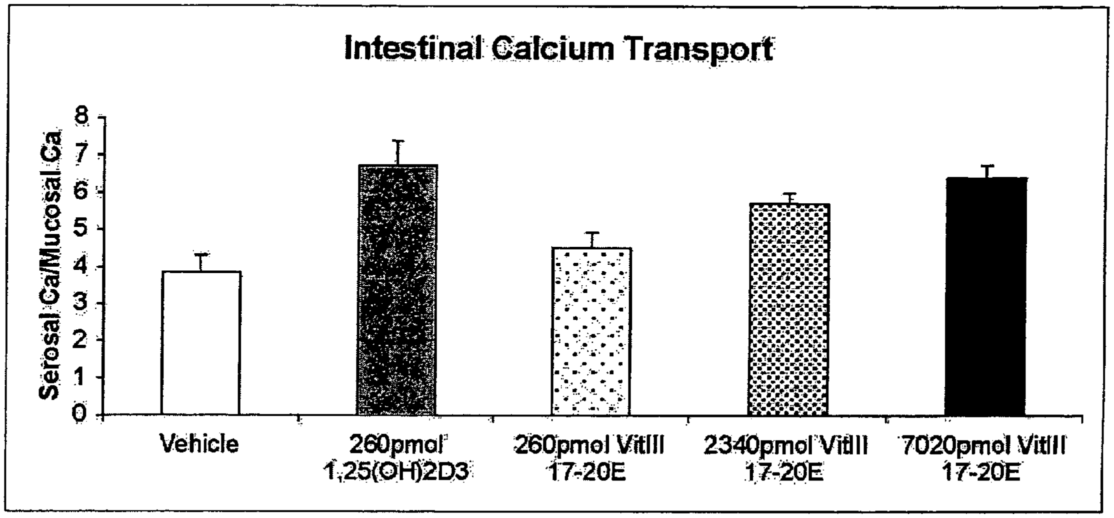

Intestinal Calcium Transport
Serosal Ca/Mucosal Ca
0
1
2
3
4
5
6
7
8
Vehicle
260pmol 1,25(OH)2D3
260pmol VitIII 17-20E
2340pmol VitIII 17-20E
7020pmol VitIII 17-20E

Figure 5

17,20(E)-DEHYDRO VITAMIN D ANALOGS AND THEIR USES

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. provisional patent application No. 60/630,007 filed Nov. 22, 2004.

BACKGROUND OF THE INVENTION

This invention relates to vitamin D compounds, and more particularly to 17,20(E)-dehydro vitamin D analogs and their pharmaceutical uses, and especially 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3, its biological activities, and its pharmaceutical uses.

The natural hormone, 1α,25-dihydroxyvitamin D_3 and its analog in the ergosterol series, i.e. 1α,25-dihydroxyvitamin D_2 are known to be highly potent regulators of calcium homeostasis in animals and humans, and their activity in cellular differentiation has also been established, Ostrem et al., Proc. Natl. Acad. Sci. USA, 84, 2610 (1987). Many structural analogs of these metabolites have been prepared and tested, including 1α-hydroxyvitamin D_3, 1α-hydroxyvitamin D_2, various side chain homologated vitamins and fluorinated analogs. Some of these compounds exhibit an interesting separation of activities in cell differentiation and calcium regulation. This difference in activity may be useful in the treatment of a variety of diseases such as renal osteodystrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies.

Another class of vitamin D analogs, i.e. the so called 19-nor-vitamin D compounds, is characterized by the replacement of the A-ring exocyclic methylene group (carbon 19), typical of the vitamin D system, by two hydrogen atoms. Biological testing of such 19-nor-analogs (e.g., 1α,25-dihydroxy-19-nor-vitamin D_3) revealed a selective activity profile with high potency in inducing cellular differentiation, and very low calcium mobilizing activity. Thus, these compounds are potentially useful as therapeutic agents for the treatment of malignancies, or the treatment of various skin disorders. Two different methods of synthesis of such 19-nor-vitamin D analogs have been described (Perlman et al., Tetrahedron Lett. 31, 1823 (1990); Perlman et al., Tetrahedron Lett. 32, 7663 (1991), and DeLuca et al., U.S. Pat. No. 5,086,191).

In U.S. Pat. No. 4,666,634, 2β-hydroxy and alkoxy (e.g., ED-71) analogs of 1α,25-dihydroxyvitamin D_3 have been described and examined by Chugai group as potential drugs for osteoporosis and as antitumor agents. See also Okano et al., Biochem. Biophys. Res. Commun. 163, 1444 (1989). Other 2-substituted (with hydroxyalkyl, e.g., ED-120, and fluoroalkyl groups) A-ring analogs of 1α,25-dihydroxyvitamin D_3 have also been prepared and tested (Miyamoto et al., Chem. Pharm. Bull. 41, 1111 (1993); Nishii et al., Osteoporosis Int. Suppl. 1, 190 (1993); Posner et al., J. Org. Chem. 59, 7855 (1994), and J. Org. Chem. 60, 4617 (1995)).

2-substituted analogs of 1α,25-dihydroxy-19-nor-vitamin D_3 have also been synthesized, i.e. compounds substituted at 2-position with hydroxy or alkoxy groups (DeLuca et al., U.S. Pat. No. 5,536,713), with 2-alkyl groups (DeLuca et al U.S. Pat. No. 5,945,410), and with 2-alkylidene groups (DeLuca et al U.S. Pat. No. 5,843,928), which exhibit interesting and selective activity profiles. All these studies indicate that binding sites in vitamin D receptors can accommodate different substituents at C-2 in the synthesized vitamin D analogs.

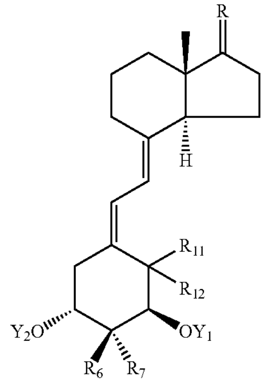
In a continuing effort to explore the 19-nor class of pharmacologically important vitamin D compounds, analogs which are characterized by the presence of a methylene substituent at carbon 2 (C-2), a hydroxyl group at carbon 1 (C-1), and a shortened side chain attached to carbon 20 (C-20) have also been synthesized and tested. 1α-hydroxy-2-methylene-19-nor-pregnacalciferol is described in U.S. Pat. No. 6,566,352 while 1α-hydroxy-2-methylene-19-nor-homopregnacalciferol is described in U.S. Pat. No. 6,579,861 and 1α-hydroxy-2-methylene-19-nor-bishomopregnacalciferol is described in U.S. Pat. No. 6,627,622. All three of these compounds have relatively high binding activity to vitamin D receptors and relatively high cell differentiation activity, but little if any calcemic activity as compared to 1α,25-dihydroxyvitamin D_3. Their biological activities make these compounds excellent candidates for a variety of pharmaceutical uses, as set forth in the '352, '861 and '622 patents.

SUMMARY OF THE INVENTION

The present invention is directed toward 17,20(E)-dehydro vitamin D analogs, and their pharmaceutical uses, and more specifically toward 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3, their biological activity, and various pharmaceutical uses for these compounds.

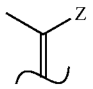
Structurally these 17,20(E)-dehydro-vitamin D analogs are characterized by the general formula I shown below:

I

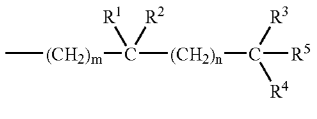


where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen or taken together are a methylene group, where R_6 and R_7, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or R_6 and R_7 when taken together may represent the group $-(CH_2)_x-$ where x is an integer from 2 to 5, or R_6 and R_7 when taken together may represent the group $=CR_8R_9$ where R_8 and R_9, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together R_8 and R_9 may represent the group $-(CH_2)_x-$ where x is an integer from 2 to 5, and where the group R represents any of the typical side chains known for vitamin D type compounds.

More specifically R can represent a saturated or unsaturated hydrocarbon radical of 1 to 35 carbons, that may be straight-chain, branched or cyclic and that may contain one or more additional substituents, such as hydroxy- or protected-hydroxy groups, fluoro, carbonyl, ester, epoxy, amino or other heteroatomic groups. Preferred side chains of this type are represented by the structure below



where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, —OY, —CH_2OY, —C≡CY and —CH═CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:

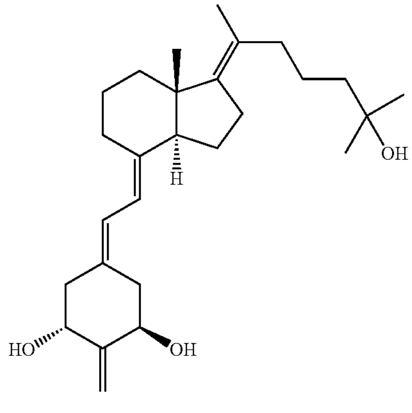


$$-(CH_2)_m-\overset{R^1\ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group having a general formula C_kH_{2k}— where k is an integer, the group $=CR^2R^3$, or the group —$(CH_2)_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —$(CH_2)_q$—, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —$CH(CH_3)$—, —$(CH_2)_m$—, —CR_1R_2— or —$(CH_2)_n$— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

The preferred analog is 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3 which has the following formula Ia:

Ia



The above compounds of formula I, especially formula Ia, exhibit a desired, and highly advantageous, pattern of biological activity. These compounds are characterized by relatively high binding to vitamin D receptors, but very low intestinal calcium transport activity, as compared to that of 1α,25-dihydroxyvitamin D_3, and have very low ability to mobilize calcium from bone, as compared to 1α,25-dihydroxyvitamin D_3. Hence, these compounds can be characterized as having little, if any, calcemic activity. It is undesirable to raise serum calcium to supraphysiologic levels when suppressing the preproparathyroid hormone gene (Darwish & DeLuca, Arch. Biochem. Biophys. 365, 123-130, 1999) and parathyroid gland proliferation. These analogs having little or no calcemic activity while being very active on cell differentiation are also expected to be useful as a therapy for suppression of secondary hyperparathyroidism of renal osteodystrophy.

The compounds I, and particularly Ia, of the invention have also been discovered to be especially suited for treatment and prophylaxis of human disorders which are characterized by an imbalance in the immune system, e.g. in autoimmune diseases, including multiple sclerosis, lupus, diabetes mellitus, host versus graft rejection, and rejection of organ transplants; and additionally for the treatment of inflammatory diseases, such as rheumatoid arthritis, asthma, and inflammatory bowel diseases such as celiac disease, ulcerative colitis and Crohn's disease. Acne, alopecia and hypertension are other conditions which may be treated with the compounds of the invention.

The above compounds I, and particularly Ia, are also characterized by relatively high cell differentiation activity. Thus, these compounds also provide therapeutic agents for the treatment of psoriasis, or as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer. In addition, due to their relatively high cell differentiation activity, these compounds provide therapeutic agents for the treatment of various skin conditions including wrinkles, lack of adequate dermal hydration, i.e. dry skin, lack of adequate skin firmness, i.e. slack skin, and insufficient sebum secretion. Use of these compounds thus not only results in moisturizing of skin but also improves the barrier function of skin.

The compounds of the invention of formula I, and particularly formula Ia, are also useful in preventing or treating obesity, inhibiting adipocyte differentiations, inhibiting SCD-1 gene transcription, and/or reducing body fat in animal subjects. Therefore, in some embodiments, a method of preventing or treating obesity, inhibiting adipocyte differentiations, inhibiting SCD-1 gene transcription, and/or reducing body fat in an animal subject includes administering to the animal subject, an effective amount of one or more of the compounds or a pharmaceutical composition that includes one or more of the compounds of formula I, and in particular the compound of formula Ia. Administration of one or more of the compounds or the pharmaceutical compositions to the subject inhibits adipocyte differentiation, inhibits gene transcription, and/or reduces body fat in the animal subject.

One or more of the compounds may be present in a composition to treat or prevent the above-noted diseases and disorders in an amount from about 0.01 μg/gm to about 1000 μg/gm of the composition, preferably from about 0.1 μg/gm to about 500 μg/gm of the composition, and may be administered topically, transdermally, orally, rectally, nasally, sublingually, or parenterally in dosages of from about 0.01 μg/day to about 1000 μg/day, preferably from about 0.1 μg/day to about 500 μg/day.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1**-**5** illustrate various biological activities of 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3, hereinafter referred to as "VIT-III," as compared to the native hormone 1α,25-dihydroxyvitamin D_3, hereinafter "$1,25(OH)_2D_3$."

FIG. **1** is a graph illustrating the relative activity of VIT-III and $1,25(OH)_2D_3$ to compete for binding with [^{3}H]-$1,25\text{-}(OH)_2\text{-}D_3$ to the full-length recombinant rat vitamin D receptor;

FIG. **2** is a graph illustrating the percent HL-60 cell differentiation as a function of the concentration of VIT-III and $1,25(OH)_2D_3$;

FIG. **3** is a graph illustrating the in vitro transcription activity of $1,25(OH)_2D_3$ as compared to VIT-III;

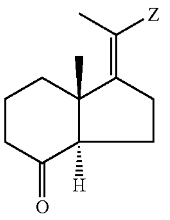
FIG. **4** is a bar graph illustrating the bone calcium mobilization activity of $1,25(OH)_2D_3$ as compared to VIT-III; and

FIG. **5** is a bar graph illustrating the intestinal calcium transport activity of $1,25(OH)_2D_3$ as compared to VIT-III.

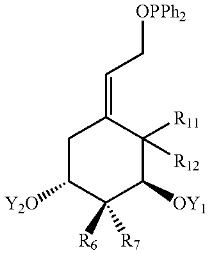
DETAILED DESCRIPTION OF THE INVENTION

The preparation of 17,20(E)-dehydro vitamin D analogs having the structure I can be accomplished by a common general method, i.e. the condensation of a bicyclic Windaus-Grundmann type ketone II with the allylic phosphine oxide III to the corresponding 17,20(E)-dehydro vitamin D analog IV followed by deprotection at C-1 and C-3 to provide I:

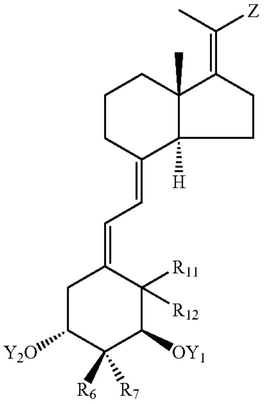
II



III



IV



In the structures III and IV, groups Y_1 and Y_2 are hydroxy-protecting groups, preferably t-butyldimethylsilyl, it being also understood that any functionalities that might be sensitive, or that interfere with the condensation reaction, be suitably protected as is well-known in the art. The process shown above represents an application of the convergent synthesis concept, which has been applied effectively for the preparation of vitamin D compounds [e.g. Lythgoe et al., J. Chem. Soc. Perkin Trans. I, 590 (1978); Lythgoe, Chem. Soc. Rev. 9, 449 (1983); Toh et al., J. Org. Chem. 48, 1414 (1983); Baggiolini et al., J. Org. Chem. 51, 3098 (1986); Sardina et al,. J. Org. Chem. 51, 1264 (1986); J. Org. Chem. 51, 1269 (1986); DeLuca et al., U.S. Pat. No. 5,086,191; DeLuca et al., U.S. Pat. No. 5,536,713].

The hydrindanones of the general structure II are not known. They can be prepared by the method shown in the Schemes herein (see the preparation of compound VIT-III).

For the preparation of the required phosphine oxides of general structure III, a synthetic route has been developed starting from a methyl quinicate derivative which is easily obtained from commercial (IR,3R,4S,5R)-(−)-quinic acid as described by Perlman et al., Tetrahedron Lett. 32, 7663 (1991) and DeLuca et al., U.S. Pat. No. 5,086,191.

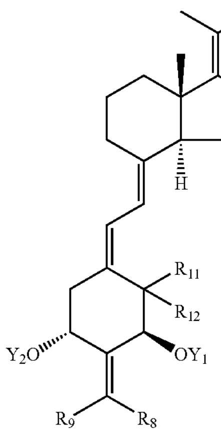
The overall process of the synthesis of compounds I and Ia is illustrated and described more completely in U.S. Pat. No. 5,843,928 entitled "2-Alkylidene-19-Nor-Vitamin D Compounds" the specification of which is specifically incorporated herein by reference.

Particularly preferred 17,20(E)-dehydro vitamin D analogs are those encompassed by general formula I wherein carbon-2 on the A-ring is substituted with an alkylidene group or an alkyl group, or are hydrolyzable slow release compounds (whether substituted at carbon-2 or not substituted at carbon-2).

2-Alkylidene Compounds

Structurally these 2-alkylidene analogs are characterized by the general formula V shown below:

V

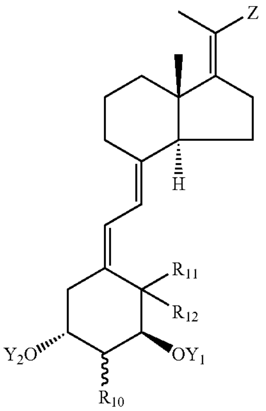


where Y_1, Y_2, R_{11}, R_{12} and Z are as previously defined herein, and R_8 and R_9, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group —$(CH_2)_x$— where x is an integer from 2 to 5.

2-Alkyl Compounds

Structurally these 2-alkyl analogs are characterized by the general formula VI shown below:

VI



where Y_1, Y_2, R_{11}, R_{12} and Z are as previously defined herein, and R_{10} is selected from the group consisting of alkyl, hydroxyalkyl and fluoroalkyl.

Slow Release Compounds

Modified vitamin D compounds that exhibit a desirable and highly advantageous pattern of biological activity in vivo, namely, the more gradual onset and more prolonged duration of activity, may also be used herein.

Structurally, the key feature of the modified vitamin D compounds having these desirable biological attributes is that they are derivatives of 17,20(E)-dehydro-vitamin D analogs, in which a hydrolyzable group is attached to the hydroxy group at carbon 25 and, optionally, to any other of the hydroxy groups present in the molecule. Depending on various structural factors—e.g. the type, size, structural complexity—of the attached group, these derivatives hydrolyze to the active 17,20(E)-dehydro-vitamin D analog, at different rates in vivo, thus providing for the "slow release" of the biologically active vitamin D compound in the body.

The "slow release" in vivo activity profiles of such compounds can, of course, be further modulated by the use of mixtures of derivatives or the use of mixtures consisting of one or more vitamin D derivative together with underivatized vitamin D compounds.

It is important to stress that the critical structural feature of the vitamin derivatives identified above is the presence of a hydrolyzable group attached to the hydroxy group at carbon 25 of the molecule. The presence of a hydrolyzable group at that position imparts on the resulting derivatives the desirable "slow-release" biological activity profile mentioned above. Other hydroxy functions occurring in the molecule (e.g. hydroxy functions at carbons 1 or 3) may be present as free hydroxy groups, or one or more of them may also be derivatived with a hydrolyzable group.

The "hydrolyzable group" present in the above-mentioned derivatives is preferably an acyl group, i.e. a group of the type Q^1CO—, where Q^1 represents hydrogen or a hydrocarbon radical of from 1 to 18 carbons that may be straight chain, cyclic, branched, saturated or unsaturated. Thus, for example, the hydrocarbon radical may be a straight chain or branched alkyl group, or a straight chain or branched alkenyl group with one or more double bonds, or it may be an optionally substituted cycloalkyl or cycloalkenyl group, or an aromatic group, such as substituted or unsubstituted phenyl, benzyl or naphthyl. Especially preferred acyl groups are alkanoyl or alkenoyl groups, of which some typical examples are formyl, acetyl, propanoyl, hexanoyl, isobutyryl, 2-butenoyl, palmitoyl or oleoyl. Another suitable type of hydrolyzable group is the hydrocarbyloxycarbonyl group, i.e. a group of the type Q^2-O—CO—, where Q^2 is a C_1 to C_{18} hydrocarbon radical as defined above. Exemplary of such hydrocarbon radicals are methyl, ethyl, propyl, and higher straight chain or branched alkyl and alkenyl radicals, as well as aromatic hydrocarbon radicals such as phenyl or benzoyl.

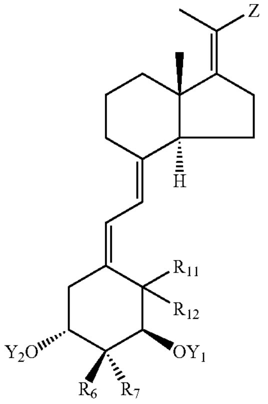
These modified vitamin D compounds are hydrolyzable in vivo to the active analog over a period of time following administration, and as a consequence regulate the in vivo availability of the active analog, thereby also modulating their activity profile in vivo. The term "activity profile" refers to the biological response over time of vitamin D compounds. Individual modified compounds, or mixtures of such compounds, can be administered to "fine tune" a desired time course of response.

As used herein the term "modified vitamin D compound" encompasses any vitamin D compound in which one or more of the hydroxy functions present in such a compound are modified by derivatization with a hydrolyzable group. A "hydrolyzable group" is a hydroxy-modifying group that can be hydrolyzed in vivo, so as to regenerate the free hydroxy functions.

In the context of this disclosure, the term hydrolyzable group preferably includes acyl and hydrocarbyloxycarbonyl groups, i.e. groups of the type Q^1CO— and Q^2-O—CO, respectively, where Q^1 and Q^2 have the meaning defining earlier.

Structurally, the modified vitamin D compounds encompassed may be represented by the formula VII shown below:

VII



where Y_1, Y_2, R_{11}, R_{12}, R_6, R_7 and Z are as previously defined herein with respect to formula I with the exception that R^5 in the side chain is —OY_3 and Y_3 is an acyl group or a hydrocarbyloxycarbonyl group, as previously defined herein.

Some specific examples of such modified vitamin D compounds include 2-substituted derivatives such as:

1,3,25-Triacetates where Y_1=Y_2=Y_3 and is CH_3CO;

1,3,25-Trihexanoates where Y_1=Y_2=Y_3 and is $CH_3(CH_2)_4CO$;

1,3,25-Trinonanoates where Y_1=Y_2=Y_3 and is $CH_3(CH_2)_7CO$; and

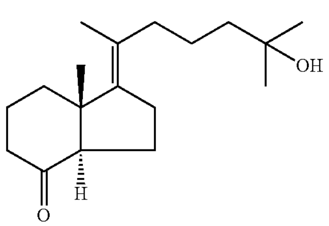
25-Acetates where Y_1=Y_2 and is H and Y_3 is CH_3CO.

These compounds can be prepared by known methods. See for example WO97/11053 published Mar. 27, 1999, and the previous description herein.

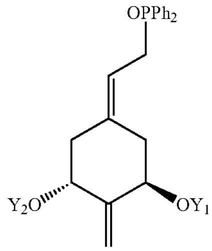
17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D$_3$ (referred to herein as VIT-III) was synthesized and tested. Structurally, this 19-nor analog is characterized by the general formula Ia previously illustrated herein.

The preparation of 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D$_3$ having the structure Ia can be accomplished by the condensation of a bicyclic Windaus-Grundmann type ketone IIa with the allylic phosphine oxide IIIa to the corresponding 17(20)-dehydro-vitamin D analog IVa followed by deprotection at C-1 and C-3 to provide Ia:

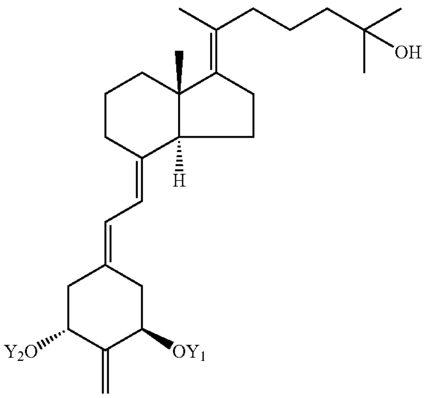
IIa



IIIa



IVa



In the structures IIIa and IVa, groups Y$_1$ and Y$_2$ are hydroxy-protecting groups, preferably t-butyldimethylsilyl, it being also understood that any functionalities that might be sensitive, or that interfere with the condensation reaction, be suitably protected as is well-known in the art. The process shown above represents a specific application of the convergent synthesis concept, which was referred to previously herein and has been applied effectively for the preparation of vitamin D compounds

The hydrindanone of the general structure IIa is not known. It can be prepared by the method shown in the Schemes herein (see the preparation of compound VIT-III).

As used in the description and in the claims, the term "hydroxy-protecting group" signifies any group commonly used for the temporary protection of hydroxy functions, such as for example, alkoxycarbonyl, acyl, alkylsilyl or alkylarylsilyl groups (hereinafter referred to simply as "silyl" groups), and alkoxyalkyl groups. Alkoxycarbonyl protecting groups are alkyl-O—CO— groupings such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or allyloxycarbonyl. The term "acyl" signifies an alkanoyl group of 1 to 6 carbons, in all of its isomeric forms, or a carboxyalkanoyl group of 1 to 6 carbons, such as an oxalyl, malonyl, succinyl, glutaryl group, or an aromatic acyl group such as benzoyl, or a halo, nitro or alkyl substituted benzoyl group. The word "alkyl" as used in the description or the claims, denotes a straight-chain or branched alkyl radical of 1 to 10 carbons, in all its isomeric forms. "Alkoxy" refers to any alkyl radical which is attached by oxygen, i.e. an alkyl-o-group. Alkoxyalkyl protecting groups are groupings such as methoxymethyl, ethoxymethyl, methoxyethoxymethyl, or tetrahydrofuranyl and tetrahydropyranyl. Preferred silyl-protecting groups are trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, dibutylmethylsilyl, diphenylmethylsilyl, phenyldimethylsilyl, diphenyl-t-butylsilyl and analogous alkylated silyl radicals. The term "aryl" specifies a phenyl-, or an alkyl-, nitro- or halo-substituted phenyl group.

A "protected hydroxy" group is a hydroxy group derivatised or protected by any of the above groups commonly used for the temporary or permanent protection of hydroxy functions, e.g. the silyl, alkoxyalkyl, acyl or alkoxycarbonyl groups, as previously defined. The terms "hydroxyalkyl", "deuteroalkyl" and "fluoroalkyl" refer to an alkyl radical substituted by one or more hydroxy, deuterium or fluoro groups respectively. An "alkylidene" refers to a radical having the general formula C_kH_{2k}—where k is an integer.

More specifically, reference should be made to the following description as well as to the Schemes herein for a detailed illustration of the preparation of compound VIT-III.

SYNTHESIS

Des-A,B-23,24-dinorcholan-8β,22-diol (2). A flame dried 1000 mL two necked flask was charged with ergocalciferol 1 (5 g, 12.6 mmol), pyridine (5 mL), and anhydrous MeOH (400 mL). The solution was cooled to −78° C. in an argon atmosphere. O_3 was bubbled through the solution until a deep blue color developed and persisted (about 1 h). The solution was treated with O_2 until the blue color faded (15 min). Then $NaBH_4$ (1.5 g, 39.7 mmol) was added. After 15 min. second portion of $NaBH_4$ (1.5 g, 39.7 mmol) was added and the reaction was allowed to warm to rt. Then the third portion of $NaBH_4$ (1.5 g, 39.7 mmol) was added and reaction stirred for over night. The reaction was quenched by adding water (50 mL). Methanol was evaporated in vaccuo and residue was dissolved in ethyl acetate. The organic phase was washed with 1N aqueous solution of HCl (100 mL), saturated $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated. Purification by silica gel chromatography (25% ethyl acetate/hexane) afforded 2.18 g (10.3 mmol, 81%) of diol 2 as a white solid. Mp 110-111° C.; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (3H, s), 1.03 (3H, d, J=6.6 Hz), 3.38 (1H, dd, J=10.5, 6.7 Hz), 3.64 (1H, dd, J=10.5, 3.2 Hz), 4.09 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 69.2, 67.8, 52.9, 52.4, 41.8, 40.2, 38.2, 33.6, 26.6, 22.6, 17.4, 16.6, 13.6; MS m/z (relative intensity): 212 (M^+, 2), 194 (M^+-H_2O, 15), 179 (M^+-H_2O—CH_3, 18), 125 (43), 111 (100); exact mass calculated for $C_{13}H_{22}O$ $[M-H_2O]^+$ is 194.1671, measured is 194.1665.

Des-A,B-22-(p-toluenesulfonyloxy)-23,24-dinorcholan-8β-ol (3). A solution of diol 2 (1 g, 4.71 mmol) in anhydrous pyridine (12 mL) was cooled to −25° C. and a precooled solution of tosyl chloride (1.08 g, 5.66 mmol) in anhydrous pyridine (2mL) was added dropwise. The reaction mixture was stirred at that temperature for 4 h and allowed to warm to 0° C. and stirred at that temperature for additional 20 h. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated $CuSO_4$ solution (30 mL), 1N HCl (30 mL), and water (50 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by silica gel chromatography (25% ethyl acetate/hexane) yielded 1.7 g (4.64 mmol, 98%) of hydroxyl tosylate 3. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, s), 0.96 (3H, d, J=6.6Hz), 2.45 (3H, s), 3.8 (1H, dd, J=9.2, 6.2 Hz), 3.95 (1H, dd, J=9.2, 3.0 Hz), 4.06 (1H, m), 7.35 (2H, d, J=8.2 Hz), 7.78 (2H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.7, 133.0, 129.8, 127.9, 75.6, 69.0, 60.4, 52.2, 41.9, 40.1, 35.7, 33.5, 26.4, 22.4, 21.6, 17.3, 16.7, 13.4; MS m/z (relative integration): 366 (M^+, 6), 194(14), 179(16), 125(30), 111(100); exact mass calculated for $C_{20}H_{30}SO_4Na$ ($M+Na^+$) is 389.1763, measured is 389.1768.

Des-A,B-8β-[(tert-butyldimethylsilyl)oxy]-22-(p-toluenesulfonyloxy)-23,24-dinorcholane (4). To a 0° C. cooled solution of hydroxyl tosylate 3 (1.5 g, 4.09 mmol) in anhydrous DMF (20 mL) was added 2,6-lutidine (0.580 mL, 0.52 g, 4.92 mmol) followed by TBSOTf (1.13 mL, 1.30 g, 4.92 mmol). The solution was stirred at 0° C. for 15 min and water (10 mL) was added. The mixture was extracted with ethyl acetate (3×40 mL), and combined organic phases were washed with 1N aqueous solution of NaOH (40 mL) dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography (5% ethyl acetate/hexane) to give 1.94 g (4.04 mmol, 99%) of 4. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.01 (6H, s), 0.88 (12H, s), 0.96 (3H, d, J=6.8 Hz), 2.45 (3H, s), 3.81 (1H, dd, J=9.2, 6.4 Hz), 3.97 (1H, dd, J=9.7, 3.0 Hz), 3.99 (1H, m), 7.34 (2H, d, J=8.08 Hz), 7.79 (2H, d, J=8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 114.5, 133.4, 129.8, 127.9, 74.8, 69.3, 52.3, 52.6, 42.2, 40.5, 35.8, 34.4, 26.6, 25.9, 23.0, 21.6, 18.0, 17.6, 16.8, 13.7, −4.8, −5.1.

Des-A,B-8β-[(tert-butyldimethylsilyl)oxy]-23,24-dinorcholan-22-al (5). A solution of 4 (1.9 g, 3.96 mmol) in DMSO (5 mL) was added to a suspension of $NaHCO_3$ (1.5 g, 17.9 mmol) in DMSO (20 mL) at rt. The mixture was heated to 150° C. under argon for 15 min and cooled to rt. Water (50 mL) followed by ethyl acetate (50 mL) were added and aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (2% ethyl acetate/hexane) to afford 0.93 g (2.87 mmol, 76%) of aldehyde 5. H NMR (400 MHz, $CDCl_3$) δ: 0.01 (6H, 2s), 0.89 (9H, s), 0.97 (3H, s), 1.09 (3H, d, J=6.8 Hz), 2.35 (1H, m), 4.03 (1H, m), 9.58 (1H, d, J=3.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.2, 69.1, 52.4, 51.8, 49.1, 42.7, 40.5, 30.8, 34.3, 26.2, 25.8, 23.3, 17.6, 14.1, 13.3, −4.7, −5.1.

Des-A,B-8β-[(tert-butyldimethylsilyl)oxy]-pregnan-20-one (6). A flame dried flask was charged with t-BuOK (1.55 g, 13.9 mmol) and anhydrous t-BuOH (30 mL) at room temperature. O_2 was bubbled through the solution for 15 min. A solution of aldehyde 5 (0.9 g, 2.78 mmol) in anhydrous t-BuOH (15 mL) was added to the reaction mixture and O_2 was bubbled through the solution for additional 10 min. The reaction was quenched with water (15 mL) and extracted with ether (3×30 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography (3% ethyl acetate/hexane) to give 0.61 g (1.97 mmol, 71%) of the ketone 6. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.01 (6H, s), 0.84 (3H, s), 0.87 (9H, s), 2.08 (3H, s), 2.46 (1H, t, J=9.1 Hz), 4.03 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.5, 69.0, 64.5, 53.2, 43.7, 39.8, 34.2, 31.6, 25.8, 23.2, 21.8, 17.6, 15.5, −4.8, −5.2.

5-Bromo-2-methyl-2-pentanol (8). To a −20° C. cooled solution of ethyl-4-bromobutyrate 7 (5 g, 25.6 mmol) in anhydrous diethyl ether (50 mL) was added 3M solution of methylmagnesium bromide in diethyl ether (17.1 mL, 6.11 g, 51.3 mmol) under argon atmosphere over a period of 30 min. The reaction mixture was stirred at room temperature for overnight. Saturated ammonium chloride solution was added to hydrolyse the reaction mixture followed by 1N HCl solution to dissolve the inorganic salts formed. The aqueous phase was extracted with ether (3×50 mL). The combined extracts were washed with water (100 mL), saturated NaCl solution (100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography (20/80 ethyl acetate/hexane) to afford 3.1 g (17.1 mmol, 67%) of tertiary alcohol. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.27 (6H, s), 1.64 (2H, m), 1.96 (2H, m), 3.44 (2H, t, J=6.68 Hz).

5-Bromo-2methyl-2[(tert-butyldimethylsilyl)oxy]-pentane (9). To a −50° C. cooled solution of alcohol 8 (3 g, 16.6 mmol) in anhydrous CH_2Cl_2 (50 mL) was added 2,6-lutidine (2.32 mL, 2.13 g, 19.89 mmol) followed by TBSOTf (4.57 mL, 5.26 g, 19.9 mmol). The solution was stirred at 0° C. for 15 min and water (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3×40 mL), and combined organic phases were washed with 1N aqueous solution of NaOH (40 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography (1% ethyl acetate/hexane) to give 3.9 g (13.2 mmol, 80%) of 9. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.07 (6H, s), 0.85 (9H, s), 1.21 (6H, s), 1.55 (2H, m), 1.95 (2H, m), 3.41 (2H, t, J=6.8 Hz)

Des-A,B-cholest-17(20)-dehydro-8β,25-diols (15a and 15b):

A solution of 5-bromo-2methyl-2[(tert-butyldimethylsilyl)oxy]pentane 9 (2.84 g, 9.68 mmol) in anhydrous ether (20 mL, containing catalytic amount of iodine) was added dropwise to a stirred suspension of magnesium powder (0.23 g, 9.68 mmol) in anhydrous diethyl ether (5 mL) at room temperature with occasional warming it up to 35° C. under argon atmosphere. After generation of the Grignard reagent was complete the mixture was stirred for 1 hr at room temperature and for 1 hr at 40° C. Then it was cooled to 0° C. and a solution of ketone 6 (0.6 g, 1.94 mmol) in anhydrous diethyl ether (10 mL) was added dropwise over a period of 30 min. After stirring the reaction mixture at room temperature for 3 h it was hydrolysed with aqueous solution of NH_4Cl (20 mL). The organic layer was separated and aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with water (40 mL), dried (Na_2SO_4) and evaporated. Silica gel column chromatography of the residue gave 0.95 g (94%) of mixture of alcohols 10. Phosphorous oxychloride (3 mL) was added dropwise to a solution of mixture of alcohols 10 (0.95 g, 1.8 mmol) in anhydrous pyridine (20 mL) under argon atmosphere. The reaction was stirred at room temperature overnight and poured into ice-water and extracted with ether (3×20 mL). The organic layer was washed with saturated $CuSO_4$ solution (30 mL), 1N HCl (30 mL), water (50 mL). The organic phase was dried ($NaSO_4$), filtered and concentrated. Column Chromatography of crude mixture furnished 0.72 g (78%) of mixture of olefins 11a, 11b, 12a, 12b, 13. The olefin mixture without further purification was dissolved in methanol (20 mL) and p-Toluenesulfonic acid monohydrate (p-TSA) (0.100 g) was added at 0° C. The reaction mixture was stirred at room temperature for 3 days

[Additional amounts of p-TSA were successively added (100 mg, 24 h; 75 mg, 36 h; 50 mg, 48 h)]. Methanol was evaporated and residue was diluted with ethyl acetate (30 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ solution (20 mL) water (20 mL), dried (Na_2CO_3) and evaporated. The residue was purified on column chromatography to yield 0.284 g (79%) of a mixture of olefin alcohols 14a, 14b, 15a, 15b, 16. The olefin alcohols were separated on HPLC.

17(E)-Des-A,B-cholestan-17(20)-dehydro-8β,25-diol (15a). The olefin alcohols were separated on HPLC (9.4 mm×25 cm zorbax-sil column, 4 ml/min) using IPA/hexane (4/96) solvent system. Pure diol 17-20E 15a 70 mg (250 μmol, 25%) was eluted at Rv=50 mL. $[\alpha]^{25}_{D}-16.5°$ (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (3H, s), 1.20 (6H, s), 1.67 (3H, t, J=1.84 Hz), 4.14 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.2, 123.7, 71.0, 69.8, 52.4, 43.9, 43.7, 38.3, 36.8, 33.4, 29.2, 28.5, 23.5, 22.2, 19.1, 17.9, 17.2. MS m/z (relative intensity): 280 (M^+, 16), 262 ($M-H_2O^+$, 7), 229 ($M-2\times H_2O—CH_3^+$, 16) 179(54), 161(100); Exact mass calculated for $C_{18}H_{32}O_2$ $[M+Na]^+$ is 303.2300, found 303.2297.

17(E)-25-(Triethylsilyloxy)-des-A,B-cholestan-17(20)-dehydro-8-one (17a). To a solution of alcohol 15a (20 mg, 71 μmol) in anhydrous CH_2Cl_2 (5 mL) was added PDC (40 mg, 107 μmol) at rt. After stirring the reaction for 3 h under argon atmosphere the solution was passed through a pad of celite with ethyl acetate. The filtrate was concentrated and applied on a Sep-Pak cartridge and eluted with ethyl acetate/hexane (20/80) to give 17 mg, (61.1 μmol, 86%) of ketone as colorless oil. To a −50° C. cooled solution of ketone (17 mg, 61.1 μmol) in anhydrous CH_2Cl_2 (5 mL) was added 2,6-lutidine (9 μL, 7.86 mg, 73.3 μmol) folowed by TESOTf (17 μL, 19.4 mg, 73.3 μmol). The solution was stirred at 0° C. for 15 min and water (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3×5 mL), and combined organic phases were dried (Na_2SO_4), filtered and concentrated. The ketone was purified on HPLC (9.4-mm×25-cm Zorbax-Sil column, 4 ml/min) using 10% ethyl acetate/hexane solvent system. Pure ketone 17a 14.4 mg (36.7 μmol, 60%) was eluted at R_v=20 mL as colorless oil. $[\alpha]^{25}_{D}-14.4$ (c 0.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.56 (6H, q, J=7.7 Hz), 0.84 (3H, s), 0.94 (9H, t, J=4.76 Hz), 1.18 (6H, s), 1.71 (3H, t, J=1.84 Hz), 2.57 (1H, dd, J=12, 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.2, 141.2, 126.1, 73.3, 61.8, 50.5, 44.7, 40.6, 36.9, 36.7, 29.9, 29.8, 28.7, 23.9, 22.1, 20.2, 17.8, 17.6, 7.1, 6.8. MS m/z (relative intensity): No M^+, 377($[M-CH_3]^+$, 3) 363($[M-C_2H_5]^+$, 9), 204(100), 189((18), 161(45). Exact mass calculated for $C_{24}H_{44}O_2Si$ $[M+Na]^+$ is 415.3008, found 415.3016.

17(E)-1α,25 Dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3 (20a). To a solution of phosphine oxide 18 (0.051 g, 87.6 μmol) in anhydrous THF (500 μL) at −25° C. was slowly added PhLi 1.2M in cyclohexane/ether (70/30) (80 μL, 8.1 mg, 96.4 μmol) under argon with stirring. The solution turned deep orange. The mixture was stirred at that temperature for 20 min and cooled to −78° C. A precooled (−78° C.) solution of ketone 17a (14 mg, 35.7 μmol) in anhydrous THF (100 μL) was added slowly. The mixture was stirred under argon atmosphere at −78° C. for 3 h and at 0° C. for 18 h. Ethyl acetate was added and organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residue was applied on a Sep-Pak cartridge, and eluted with 1% ethyl acetate/hexane to give 19-nor protected vitamin derivative 19a (8 mg of unreacted ketone 17a was recovered). The protected vitamin was further purified by HPLC (9.4-mm×25-cm Zorbax-Sil column, 4 ml/min) using hexane/IPA (99.95/0.05) solvent system. Pure compound 19a, 7.7 mg (10.2 μmol, 29%) was eluted at R_v=20 mL as colorless oil. UV (in hexane) λ_{max} 243.1, 252, 262.2 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.03, 0.05, 0.07, 0.08 (each 3H, each s), 0.56 (6H, q, J=7.8 Hz), 0.74 (3H, s), 0.87 and 0.91 (each 9H, each s), 0.96 (9H, t, J=7.8 Hz), 1.19 (6H, s), 1.68(3H, t, J=1.86 Hz), 2.18 (1H, dd, J=12.6, 8.3 Hz), 2.33 (1H, m) 2.46 (1H, dd, 12.6, 4.6 Hz), 2.53 (1H, dd, 13.3, 5.88 Hz), 2.80 (1H, m), 4.43 (2H, m), 4.93 and 4.97 (1H and 1H, each s), 5.88 and 6.21 (1H and 1H, each d, J=11.2 Hz); MS m/z (relative intensity): No M^+, 624(59), 366(32), 91(100); Exact mass calculated for $C_{45}H_{84}O_3Si_3$ $[M+Na]^+$ is 779.5626, found 779.5648.

The protected vitamin 19a (7.7 mg, 10.2 μmol) was dissolved in anhydrous THF (500 μL) and treated with TBAF (0.102 mL, 26.7 mg, 102 μmol) and stirred at rt in dark for overnight. The solvent was removed in vaccuo and residue was applied on Sep-Pak cartridge, and eluted with 30% ethyl acetate/hexane to get the deprotected vitamin 20a. The vitamin was further purified by HPLC (9.4-mm×25-cm Zorbax-Sil column, 3 mL/min) using hexane/IPA (90/10) as solvent system. Pure vitamin 20a, 2.9 mg (7 μmol, 69%) was collected at R_v=42 mL as white solid: UV (in EtOH) λ_{max} 242.9, 251, 261.2 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.74 (3H, s), 1.22 (6H, s), 1.69 (3H, t, J=1.94 Hz,), 2.29 (1H, dd, J=13.0, 8.39 Hz), 2.32 (1H, dd, J=13.9, 7.0 Hz), 2.57 (1H, dd, J=13.4, 3.49 Hz), 2.79 (1H, br d) 2.87(1H, dd, J=13.0, 4.59 Hz), 4.49 (2H, m), 5.09 and 5.11 (1H and 1H, each s), 5.92 and 6.35 (1H and 1H, each d, J=11.29 Hz); MS m/z (relative intensity): 414 (M^+, 36), 396($[M-H_2O]$+, 6), 381 ($[M-H_2O—CH_3]^+$, 8) 285(70), 149(61), 69(100).

17(Z)-Des-A,B-cholest-17(20)-dehydro-8β,25-diol (15b). The olefin alcohols were separated on HPLC (9.4 mm×25 cm zorbax-sil column, 4 ml/min) using IPA/hexane (5/95) solvent system. Diol 17-20Z 15b and Diol 20-21 16 eluted out together at Rv=45 mL. The alcohols were oxidized together.

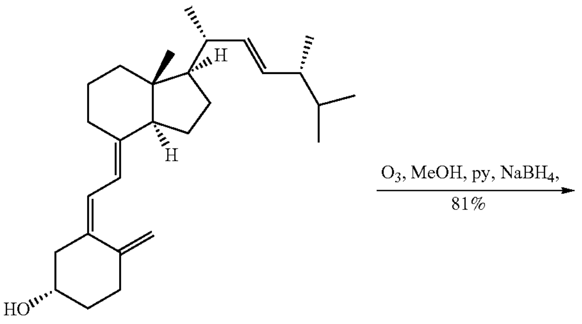
17(Z)-25-(Triethylsilyloxy)-des-A,B-cholest-17(20)-dehydro-8-one (17b). To a solution of mixture of alcohols 15b and 16 (34 mg, 121 μmol) in anhydrous CH_2Cl_2 (5 mL) was added PDC (55 mg, 145.7 μmol) at rt. After stirring the reaction for 3 h under argon atmosphere the solution was passed through a pad of celite with ethyl acetate. The filtrate was concentrated and applied on a Sep-Pak cartridge and eluted with ethyl acetate/hexane (20/80) to give a mixture of ketones 17b and 16b 30.2 mg (108.6 μmol, 89%) as colorless oil. To a −50° C. cooled solution of ketones 30.2 mg (30.2 mg, 108.6 μmol) in anhydrous CH_2Cl_2 (10 mL) was added 2,6-lutidine (16 μL, 13.9 mg, 130.3 μmol) followed by TESOTf (30 μL, 34.5 mg, 130.3 μmol). The solution was stirred at 0° C. for 15 min and water (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3×5 mL), and combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by HPLC (9.4-mm×25-cm Zorbax-Sil column, 4 ml/min) using ethyl acetate/hexane (5/95) solvent system. Pure ketone 17b 7.7 mg (19.6 μmol, 18%) was eluted at R_v=34 mL as colorless oil. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 0.56 (6H, q, J=7.78 Hz), 0.83 (3H, s), 0.94 (9H, t, J=7.9 Hz), 1.2 (6H, s), 1.57 (3H, br s), 2.57 (1H, dd, J=11.8, 6.3 Hz); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 212.18, 141.1, 126.8, 73.2, 62.0, 50.5, 45.3, 40.7, 37.1, 34.5, 29.9, 29.8, 24.0, 23.8, 20.2, 20.1, 18.7, 7.1, 6.8. MS m/z (relative intensity): No M^+, 363 ($[M-C_2H_5]^+$, 10), 334 ($[M-2\times C_2H_5]^+$, 1), 204 (100).

17(Z)-1α,25 Dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3 (20b). To a solution of phosphine oxide 10 (62 mg, 106.5 μmol) in anhydrous THF (750 μL) at −25° C. was slowly added PhLi 1.8 M in Di-n-butyl ether (59 μL, 8.9 mg, 106.5 μmol) under argon with stirring. The solution turned deep orange. The mixture was stirred at that temperature for 20 min and cooled to −78° C. A precooled (−78° C.) solution of ketone 17b (7.7 mg, 19.6 μmol) in anhydrous THF (100 μL) was added slowly. The mixture was stirred under argon atmosphere at −78° C. for 3 h and at 0° C. for 18 h. Ethyl acetate was added and organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residue was applied on a Sep-Pak cartridge, and eluted with 1% ethyl acetate/hexane to give the 19-nor protected vitamin derivative. The vitamin was further purified by HPLC (9.4-mm× 25-cm Zorbax-Sil column, 4 ml/min) using hexane/IPA (99.95:0.05) solvent system. Pure compound 19b, 12.8 mg (16.9 μmol, 86%) was eluted at R_v=19 mL as colorless oil. $[\alpha]^{25}_{D}$−9.35 (c 0.64, $CHCl_3$); UV (in hexane): λ_{max} 244.4, 253.2, 263.2 nm; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.026, 0.050, 0.067, 0.082 (each 3H, each s), 0.56 (6H, q, J=7.84 Hz), 0.74 (3H, s), 0.86, 0.89 (each 9H, each s), 0.94 (9H, t, J=7.96 Hz), 1.19 (6H, s), 1.56 (3H, br s), 2.14 (1H, dd, J=12.5, 4.8 Hz), 2.33 (1H, dd, J=13.1, 2.8 Hz), 2.46 (1H, dd, J=12.7, 4.4 Hz), 2.53 (1H, dd, J=13.3, 6.0 Hz), 2.80 (1H, br d, J=13.5 Hz), 4.43 (2H, m), 4.92 and 4.97 (each 1H, each s), 5.88 and 6.21 (each 1H, each d, J=11.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.9, 142.2, 140.8, 132.8, 125.9, 122.3, 116.3, 106.2, 73.3, 72.5, 71.6, 56.7, 47.6, 46.8, 45.4, 30.1, 29.8, 28.5, 25.8, 25.7, 23.9, 23.6, 23.0, 19.9, 18.2, 18.1, 17.8, 7.1, 6.8, −4.8, −5.0; MS m/z (relative intensity): No M^+, 366(2), 263(100); Exact mass calculated for $C_{45}H_{84}O_3Si_3[M+Na]^+$ is 779.5626, found 779.5647.

The protected vitamin 19b (12.8 mg, 16.9 mmol) was dissolved in anhydrous THF (500 μL) and treated with TBAF (170 μL, 44.2 mg, 169 μmol) and stirred at rt in dark for overnight. The solvent was removed in vaccuo and residue was applied on Sep-Pak cartridge, and eluted with 30% ethyl acetate/hexane to get the deprotected vitamin. The vitamin was further purified by HPLC (9.4-mm×25-cm Zorbax-Sil column, 4 ml/min) using hexane/IPA (85/15) as solvent system. Pure vitamin 20b, 4.3 mg (10.3 μmol, 62%) was eluted at R_v=33 mL. UV (in ethanol): λ_{max} 244.1, 252.5, 262.1 nm; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.74 (3H, s), 1.21 (6H, s), 1.57 (3H, br s), 2.30 (2H, m), 2.57 (1H, dd, J=13.3, 3.6 Hz), 2.79 (1H, dd, J=11.6, 2.52 Hz), 2.85 (1H, dd, J=13.1, 4.44 Hz), 4.48 (2H, m), 5.09 and 5.11 (1H and 1H, each s), 5.92 and 6.35 (1H and 1H, each d, J=11.3 Hz); MS m/z (relative intensity): 414 (M^+, 90), 399 ($M-CH_3^+$, 17), 381 $[M-CH_3—H_2O]^+$, 18), 363 ($[M-CH_3\text{-}2\times H_2O]^+$, 7), 285 (86), 243 (35), 91 (100); exact mass calculated for $C_{27}H_{42}O_3$ ($[M+Na]^+$) is 437.3032, measured is 437.3026.

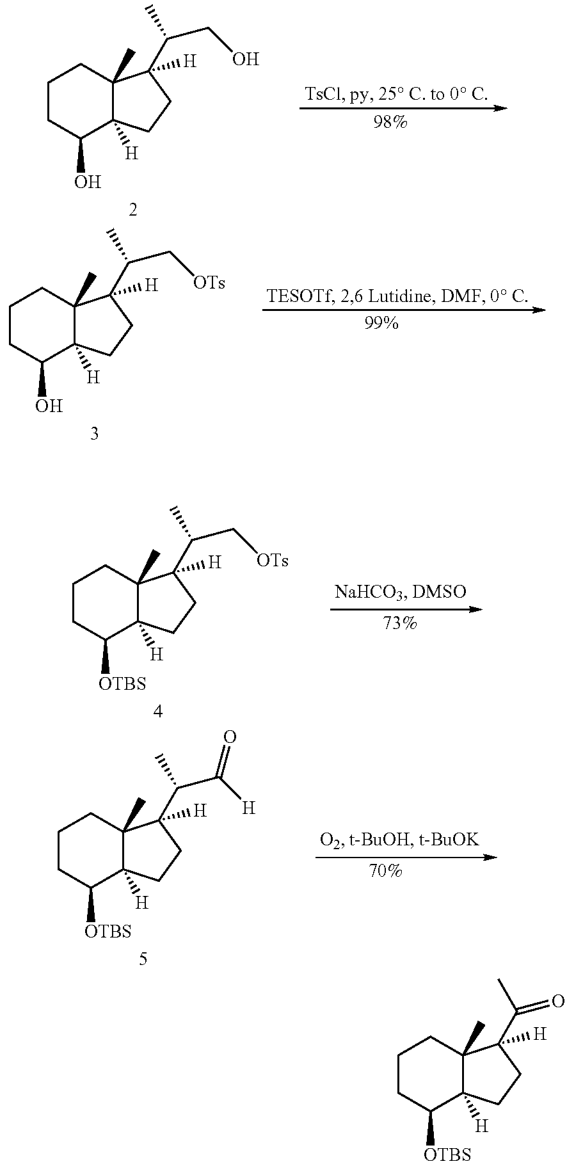
SCHEMES

Scheme- I

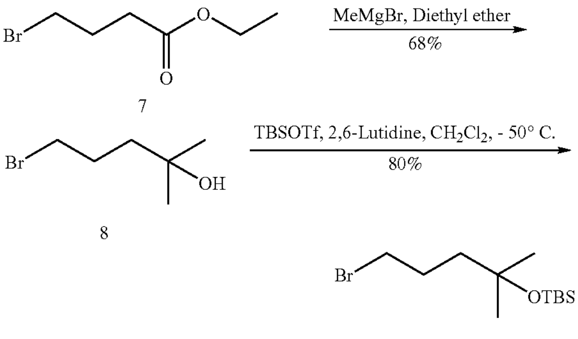


1

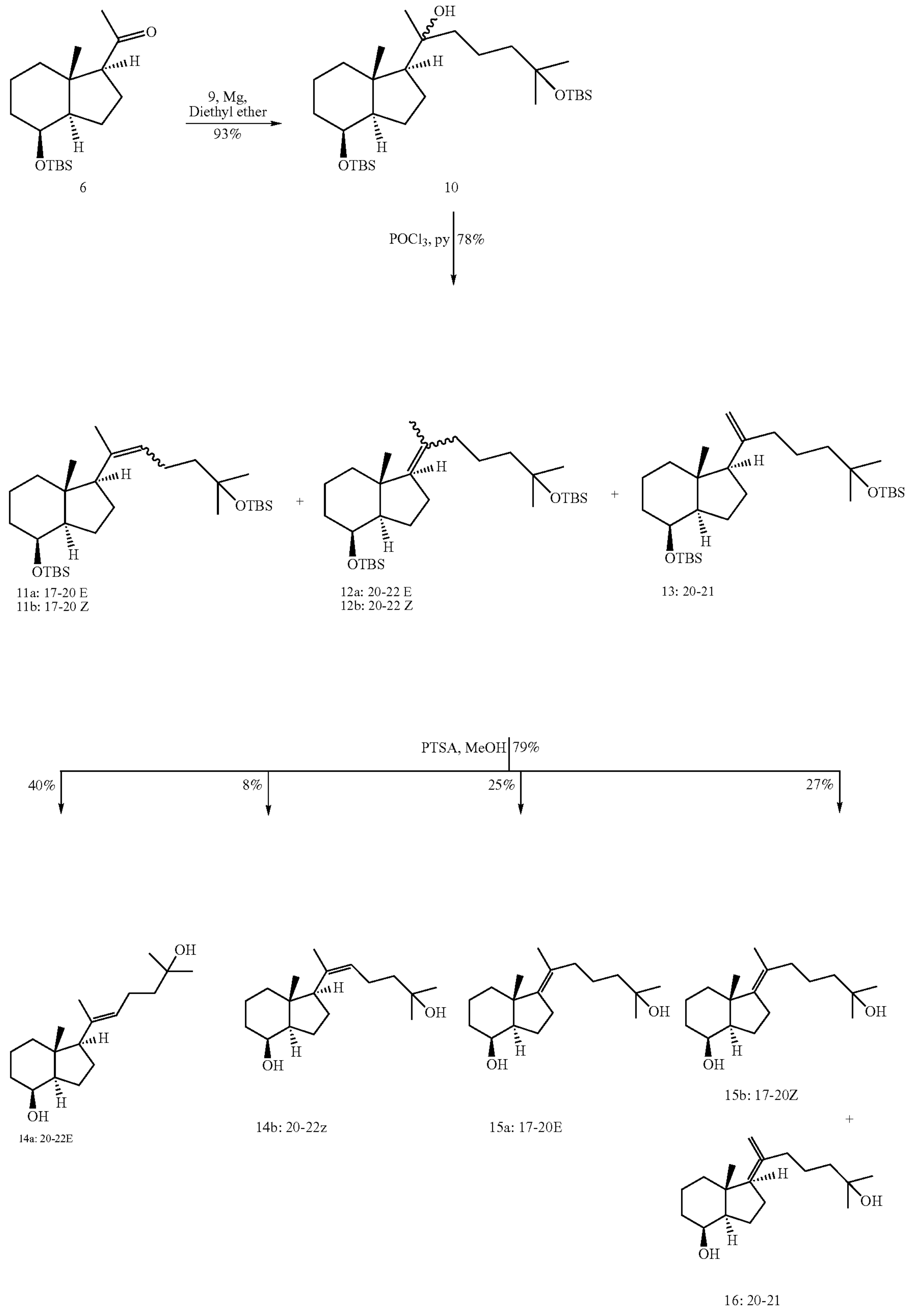
-continued



Scheme - II

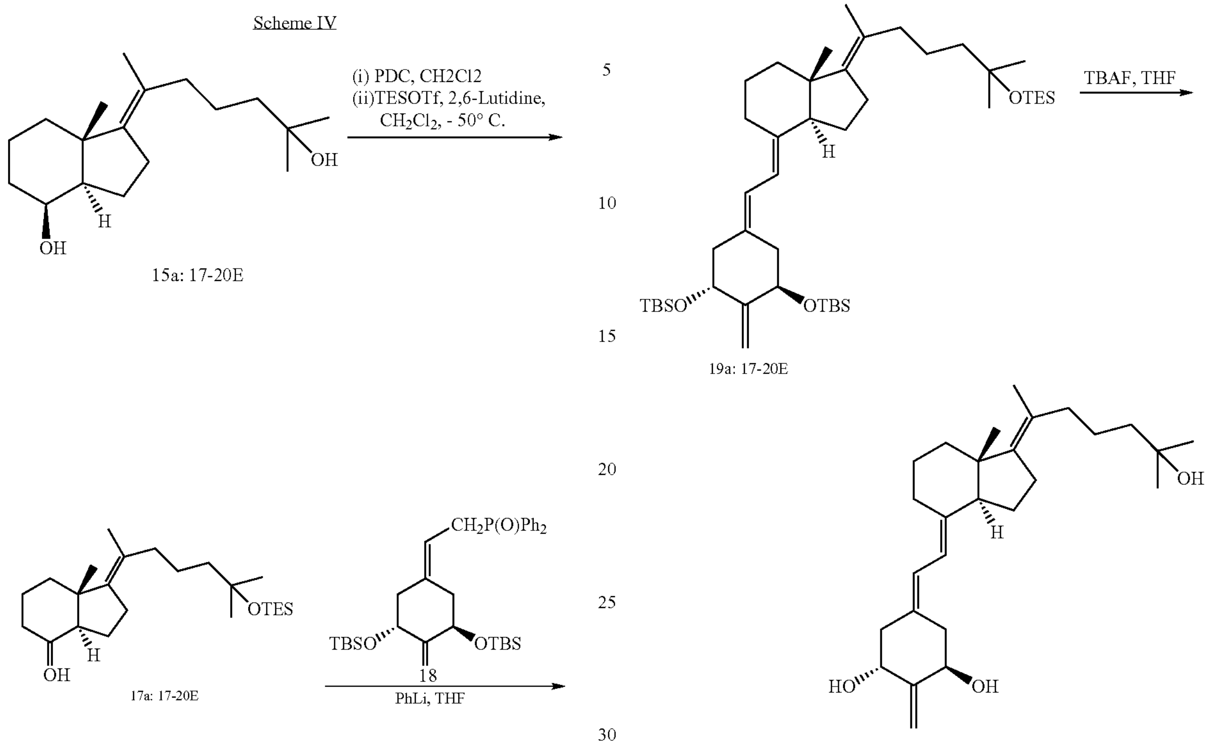


Scheme III


6
9, Mg,
Diethyl ether
93%
10
POCl3, py
78%
11a: 17-20 E
11b: 17-20 Z
+
12a: 20-22 E
12b: 20-22 Z
+
13: 20-21
PTSA, MeOH
79%
40%
8%
25%
27%
14a: 20-22E
14b: 20-22z
15a: 17-20E
15b: 17-20Z
+
16: 20-21
OTBS
OH
H
O

-continued

Scheme IV



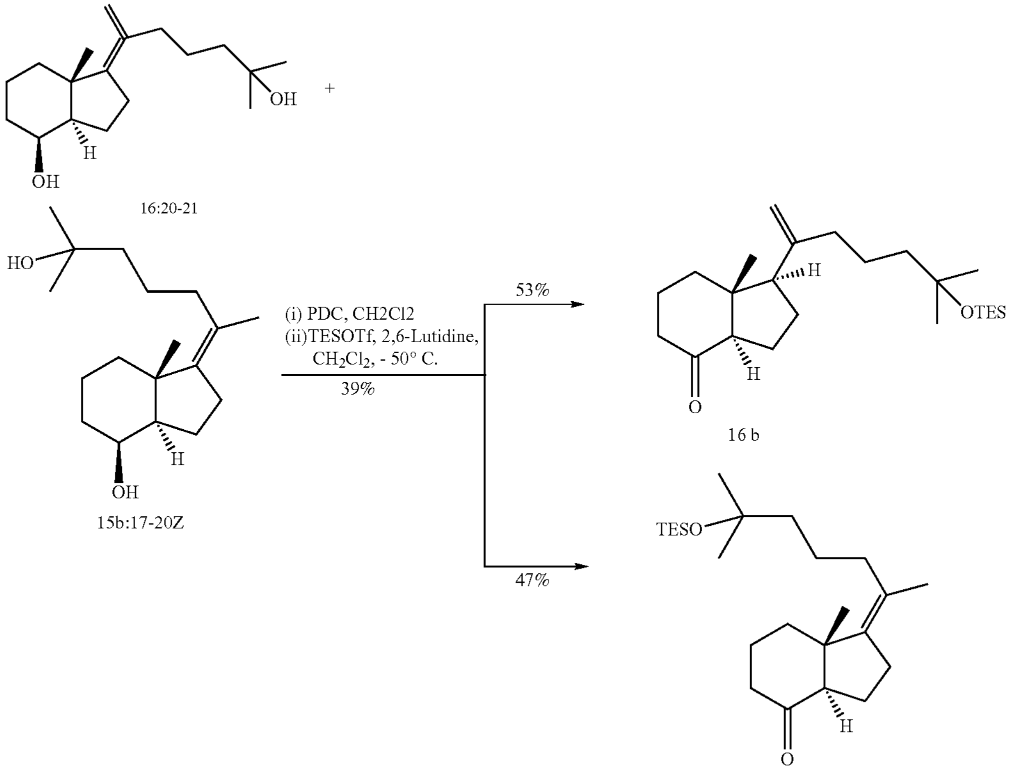
15a: 17-20E

19a: 17-20E

17a: 17-20E

20a: 17-20E

Scheme - V



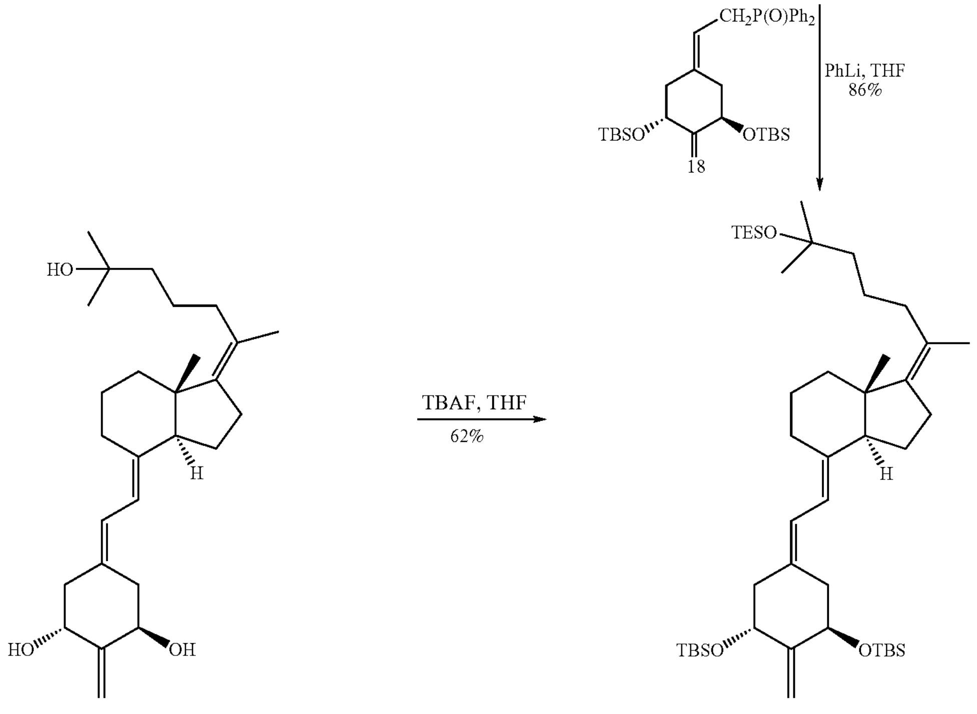
16:20-21

15b:17-20Z

16 b

17b:17-20Z

-continued



20a: 17-20E

19b: 17-20Z

BIOLOGICAL ACTIVITY OF 17(E)-1α,25-DIHYDROXY-17(20)-DEHYDRO-2-METHYLENE-19-NORVITAMIN D_3

The introduction of a methylene group to the 2-position, the introduction of a double bond between the 17 and 20 positions, and orientating the side chain of 1α,25-dihydroxy-19-nor-vitamin D_3 in its E configuration had little or no effect on binding to the full length recombinant rat vitamin D receptor, as compared to 1α,25-dihydroxyvitamin D_3. The compound VIT-III bound equally well to the receptor as compared to the standard 1,25-$(OH)_2D_3$ (FIG. **1**). It might be expected from these results that compound VIT-III would have equivalent biological activity. Surprisingly, however, compound VIT-III is a highly selective analog with unique biological activity.

FIG. **5** shows that VIT-III has little activity as compared to that of 1,25-dihydroxyvitamin D_3 (1,25$(OH)_2D_3$), the natural hormone, in stimulating intestinal calcium transport.

FIG. **4** demonstrates that VIT-III has very little bone calcium mobilization activity, as compared to 1,25$(OH)_2D_3$.

FIGS. **4**-**5** thus illustrate that VIT-III may be characterized as having little, if any, calcemic activity.

FIG. **2** illustrates that VIT-III is as potent as 1,25$(OH)_2D_3$ on HL-60 cell differentiation, making it an excellent candidate for the treatment of psoriasis and cancer, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer. In addition, due to its relatively high cell differentiation activity, this compound provides a therapeutic agent for the treatment of various skin conditions including wrinkles, lack of adequate dermal hydration, i.e. dry skin, lack of adequate skin firmness, i.e. slack skin, and insufficient sebum secretion. Use of this compound thus not only results in moisturizing of skin but also improves the barrier function of skin.

FIG. **3** illustrates that the compound VIT-III has about the same transcriptional activity as 1α,25-dihydroxyvitamin D_3 in bone cells. This result, together with the cell differentiation activity of FIG. **2**, suggests that VIT-III will be very effective in psoriasis because it has direct cellular activity in causing cell differentiation and in suppressing cell growth. These data also indicate that VIT-111 may have significant activity as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer.

The strong activity of VIT-III on HL-60 differentiation suggests it will be active in suppressing growth of parathyroid glands and in the suppression of the preproparathyroid gene.

Experimental Methods

The compounds of the invention were prepared and studied using the following methods.

Vitamin D Receptor Binding

Test Material

Protein Source

Full-length recombinant rat receptor was expressed in *E. coli* BL21 (DE3) Codon Plus RIL cells and purified to homogeneity using two different column chromatography systems. The first system was a nickel affinity resin that utilizes the C-terminal histidine tag on this protein. The protein that was eluted from this resin was further purified using ion exchange chromatography (S-Sepharose Fast Flow). Aliquots of the purified protein were quick frozen in liquid nitrogen and stored at −80° C. until use. For use in binding assays, the protein was diluted in $TEDK_{50}$ (50 mM Tris, 1.5 mM EDTA, pH7.4, 5 mM DTT, 150 mM KCl) with 0.1% Chaps detergent. The receptor protein and ligand concentration was optimized such that no more than 20% of the added radiolabeled ligand was bound to the receptor.

Study Drugs

Unlabeled ligands were dissolved in ethanol and the concentrations determined using UV spectrophotometry ($1,25(OH)_2D_3$: molar extinction coefficient=18,200 and λ_{max}=265 nm). Radiolabeled ligand ($3H-1,25(OH)_2D_3$, ~159 Ci/mmole) was added in ethanol at a final concentration of 1 nM.

Assay Conditions

Radiolabeled and unlabeled ligands were added to 100 mcl of the diluted protein at a final ethanol concentration of ≦10%, mixed and incubated overnight on ice to reach binding equilibrium. The following day, 100 mcl of hydroxylapatite slurry (50%) was added to each tube and mixed at 10-minute intervals for 30 minutes. The hydroxylapaptite was collected by centrifugation and then washed three times with Tris-EDTA buffer (50 mM Tris, 1.5 mM EDTA, pH 7.4) containing 0.5%. Titron X-100. After the final wash, the pellets were transferred to scintillation vials containing 4 ml of Biosafe II scintillation cocktail, mixed and placed in a scintillation counter. Total binding was determined from the tubes containing only radiolabeled ligand.

HL-60 Differentiation

Test Material

Study Drugs

The study drugs were dissolved in ethanol and the concentrations determined using UV spectrophotometry. Serial dilutions were prepared so that a range of drug concentrations could be tested without changing the final concentration of ethanol (≦0.2%) present in the cell cultures.

Cells

Human promyelocytic leukemia (HL60) cells were grown in RPMI-1640 medium containing 10% fetal bovine serum. The cells were incubated at 37° C. in the presence of 5% CO_2.

Assay Conditions

HL60 cells were plated at 1.2×10^5 cells/ml. Eighteen hours after plating, cells in duplicate were treated with drug. Four days later, the cells were harvested and a nitro blue tetrazolium reduction assay was performed (Collins et al., 1979; J. Exp. Med. 149:969-974). The percentage of differentiated cells was determined by counting a total of 200 cells and recording the number that contained intracellular black-blue formazan deposits. Verification of differentiation to monocytic cells was determined by measuring phagocytic activity (data not shown).

In vitro Transcription Assay

Transcription activity was measured in ROS 17/2.8 (bone) cells that were stably transfected with a 24-hydroxylase (24Ohase) gene promoter upstream of a luciferase reporter gene (Arbour et al., 1998). Cells were given a range of doses. Sixteen hours after dosing the cells were harvested and luciferase activities were measured using a luminometer. RLU=relative luciferase units.

Antagonism was tested by adding a combination of $1,25(OH)_2D_3$ and the compound in the same well keeping the final ethanol concentration the same.

Intestinal Calcium Transport and Bone Calcium Mobilization

Male, weanling Sprague-Dawley rats were placed on Diet 11 (Suda et al, J. Nutr. 100:1049, 1970) (0.47% Ca)+vitamins AEK for one week followed by Diet 11 (0.02% Ca)+vitamins AEK for 3 weeks. The rats were then switched to the same diet containing 0.47% Ca for one week followed by two weeks on the same diet containing 0.02% Ca. Dose administration began during the last week on 0.02% calcium diet. Four consecutive ip doses were given approximately 24 hours apart. Twenty-four hours after the last dose, blood was collected from the severed neck and the concentration of serum calcium determined by atomic absorption spectrometry as a measure of bone calcium mobilization. The first 10 cm of the intestine was also collected for intestinal calcium transport analysis using the everted gut sac method.

Antagonism was tested by administering a combination of $1,25(OH)_2D_3$ and the compound to the animal simultaneously.

Interpretation of Data

VDR binding, HL60 cell differentiation, and transcription activity. VIT-III (K_i=3.8×10^{-10}M) is equivalent to the natural hormone 1α,25-dihydroxyvitamin D_3 (K_i=$1.\times10^{-10}$M) in its ability to compete with $[^3H]-1,25(OH)_2D_3$ for binding to the full-length recombinant rat vitamin D receptor (FIG. **1**). There is also little difference between VIT-III (EC_{50}=1.7×10^{-8}M) in its ability (efficacy or potency) to promote HL60 differentiation as compared to 1α,25-dihydroxyvitamin D_3 (EC_{50}=2.8×10^{-8}M) (See FIG. **2**). Also, compound VIT-III (EC_{50}=3.1×10^{-11}M) has about the same transcriptional activity in bone cells as 1α,25-dihydroxyvitamin D_3 (EC_{50}=2.3×10^{-10}M) (See FIG. **3**). These results suggest that VIT-III will be very effective in psoriasis because it has direct cellular activity in causing cell differentiation and in suppressing cell growth. These data also indicate that VIT-III will have significant activity as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer, as well as against skin conditions such as dry skin (lack of dermal hydration), undue skin slackness (insufficient skin firmness), insufficient sebum secretion and wrinkles. It would also be expected to be very active in suppressing secondary hyperparathyroidism.

Calcium mobilization from bone and intestinal calcium absorption in vitamin D-deficient animals. Using vitamin D-deficient rats on a low calcium diet (0.02%), the activities of VIT-III and $1,25(OH)_2D_3$ in intestine and bone were tested. As expected, the native hormone ($1,25(OH)_2D_3$) increased serum calcium levels at all dosages (FIG. **4**). FIG. **4** shows that VIT-III has little, if any, activity in mobilizing calcium from bone. Administration of VIT-III at 260 pmol/day for 4 consecutive days did not result in mobilization of bone calcium, and increasing the amount of VIT-III to 2340 pmol/day and then to 7020 pmol/day was also without any substantial effect.

Intestinal calcium transport was evaluated in the same groups of animals using the everted gut sac method (FIG. **5**). These results show that the compound VIT-III does not promote intestinal calcium transport when administered at 260 pmol/day, and has slight activity at 2340 pmol/day and does show some activity at 7020 pmol/day, whereas $1,25(OH)_2D_3$ promotes a significant increase at the 260 pmol/day dose. Thus, it may be concluded that VIT-III is essentially devoid of intestinal calcium transport activity at the tested doses.

These results illustrate that VIT-III is an excellent candidate for numerous human therapies as described herein, and that it may be particularly useful in a number of circumstances such as suppression of secondary hyperparathyroidism of renal osteodystrophy, autoimmune diseases, cancer, and psoriasis. VIT-III is an excellent candidate for treating psoriasis because: (1) it has significant VDR binding, transcription activity and cellular differentiation activity; (2) it is devoid of hypercalcemic liability unlike $1,25(OH)_2D_3$; and (3) it is easily synthesized. Since VIT-III has significant binding activity to the vitamin D receptor, but has little ability to raise blood serum calcium, it may also be particularly useful for the treatment of secondary hyperparathyroidism of renal osteodystrophy.

These data also indicate that the compound VIT-III of the invention may be especially suited for treatment and prophylaxis of human disorders which are characterized by an imbalance in the immune system, e.g. in autoimmune diseases, including multiple sclerosis, lupus, diabetes mellitus, host versus graft rejection, and rejection of organ transplants; and additionally for the treatment of inflammatory diseases, such as rheumatoid arthritis, asthma, and inflammatory bowel diseases such as celiac disease, ulcerative colitis and Crohn's disease. Acne, alopecia and hypertension are other conditions which may be treated with the compound VIT-III of the invention.

The compounds of the invention of formula I, and particularly formula la, are also useful in preventing or treating obesity, inhibiting adipocyte differentiations, inhibiting SCD-1 gene transcription, and/or reducing body fat in animal subjects. Therefore, in some embodiments, a method of preventing or treating obesity, inhibiting adipocyte differentiations, inhibiting SCD-1 gene transcription, and/or reducing body fat in an animal subject includes administering to the animal subject, an effective amount of one or more of the compounds or a pharmaceutical composition that includes one or more of the compounds of formula I. Administration of one or more of the compounds or the pharmaceutical compositions to the subject inhibits adipocyte differentiation, inhibits gene transcription, and/or reduces body fat in the animal subject. The animal may be a human, a domestic animal such as a dog or a cat, or an agricultural animal, especially those that provide meat for human consumption, such as fowl like chickens, turkeys, pheasant or quail, as well as bovine, ovine, caprine, or porcine animals.

For prevention and/or treatment purposes, the compounds of this invention defined by formula I and Ia may be formulated for pharmaceutical applications as a solution in innocuous solvents, or as an emulsion, suspension or dispersion in suitable solvents or carriers, or as pills, tablets or capsules, together with solid carriers, according to conventional methods known in the art. Any such formulations may also contain other pharmaceutically-acceptable and nontoxic excipients such as stabilizers, anti-oxidants, binders, coloring agents or emulsifying or taste-modifying agents.

The compounds of formula I and particularly VIT-III of formula Ia, may be administered orally, topically, parenterally, rectally, nasally, sublingually, or transdermally. The compound is advantageously administered by injection or by intravenous infusion or suitable sterile solutions, or in the form of liquid or solid doses via the alimentary canal, or in the form of creams, ointments, patches, or similar vehicles suitable for transdermal applications. A dose of from 0.01 μg to 1000 μg per day of the compounds I, particularly VIT-III, preferably from about 0.1 μg to about 500 μg per day, is appropriate for prevention and/or treatment purposes, such dose being adjusted according to the disease to be treated, its severity and the response of the subject as is well understood in the art. Since the compound exhibits specificity of action, each may be suitably administered alone, or together with graded doses of another active vitamin D compound—e.g. 1α-hydroxyvitamin D_2 or D_3, or 1α,25-dihydroxyvitamin D_3—in situations where different degrees of bone mineral mobilization and calcium transport stimulation is found to be advantageous.

Compositions for use in the above-mentioned treatments comprise an effective amount of the compounds I, particularly VIT-III, as defined by the above formula I and Ia as the active ingredient, and a suitable carrier. An effective amount of such compound for use in accordance with this invention is from about 0.01 μg to about 1000 μg per gm of composition, preferably from about 0.1 μg to about 500 μg per gram of composition, and may be administered topically, transdermally, orally, rectally, nasally, sublingually, or parenterally in dosages of from about 0.01 μg/day to about 1000 μg /day, and preferably from about 0.1 μg/day to about 500 μg/day.

The compounds I, particularly VIT-III, may be formulated as creams, lotions, ointments, topical patches, pills, capsules or tablets, suppositories, aerosols, or in liquid form as solutions, emulsions, dispersions, or suspensions in pharmaceutically innocuous and acceptable solvent or oils, and such preparations may contain in addition other pharmaceutically innocuous or beneficial components, such as stabilizers, antioxidants, emulsifiers, coloring agents, binders or taste-modifying agents.

The compounds I, particularly VIT-III, may be advantageously administered in amounts sufficient to effect the differentiation of promyelocytes to normal macrophages. Dosages as described above are suitable, it being understood that the amounts given are to be adjusted in accordance with the severity of the disease, and the condition and response of the subject as is well understood in the art.

The formulations of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

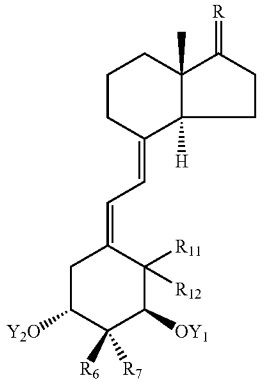
Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops; or as sprays.

For nasal administration, inhalation of powder, self-propelling or spray formulations, dispensed with a spray can, a nebulizer or an atomizer can be used. The formulations, when dispensed, preferably have a particle size in the range of 10 to 100μ.

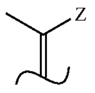
The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient as a physically and chemically stable unit dose comprising either the active ingredient as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

What is claimed is:

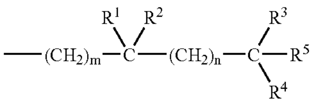
1. A compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen, where R_6 and R_7, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or R_6 and R_7 when taken together may represent the group $—(CH_2)_x—$ where x is an integer from 2 to 5, or R_6 and R_7 when taken together may represent the group $=CR_8R_9$ where R_8 and R_9, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together R_8 and R_9 may represent the group $—(CH_2)_x—$ where x is an integer from 2 to 5, and where the group R represents a side chain represented by the structure



where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, —OY, $—CH_2OY$, —C≡CY and —CH═CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $—COR^5$ and a radical of the structure:



$$—(CH_2)_m—\overset{R^1\ R^2}{C}—(CH_2)_n—\underset{R^4}{\overset{R^3}{C}}—R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group having a general formula $C_kH_{2k}—$ where k is an integer, the group $=CR^2R^3$, or the group $—(CH_2)_p—$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $—(CH_2)_q—$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $—CH(CH_3)—$, $—(CH_2)_m—$, $—CR_1R_2—$ or $—(CH_2)_n—$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

2. The compound of claim **1** wherein Y_2 is hydrogen.

3. The compound of claim **1** wherein Y_1 is hydrogen.

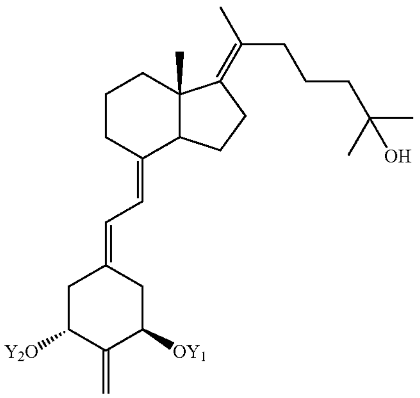
4. The compound of claim **1** wherein Y_1, Y_2 and R^5 are hydrogen.

5. A pharmaceutical composition containing an effective amount of at least one compound as claimed in claim **1** together with a pharmaceutically acceptable excipient.

6. The pharmaceutical composition of claim **5** wherein said effective amount comprises from about 0.01 μg to about 1000 μg per gram of composition.

7. The pharmaceutical composition of claim **5** wherein said effective amount comprises from about 0.1 μg to about 500 μg per gram of composition.

8. A compound having the formula:



where the 17-ene double bond and side chain are in the E configuration, and where Y_1 and Y_2, which may be the same or different, are each selected from hydrogen or a hydroxy-protecting group.

9. The compound of claim **8** wherein Y_2 is hydrogen.

10. The compound of claim **8** wherein Y_1 is hydrogen.

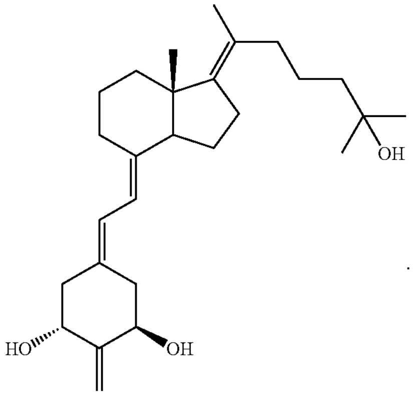
11. The compound of claim **8** wherein Y_1 and Y_2 are both t-butyldimethylsilyl.

12. A pharmaceutical composition containing an effective amount of at least one compound as claimed in claim **8** together with a pharmaceutically acceptable excipient.

13. The pharmaceutical composition of claim **12** wherein said effective amount comprises from about 0.01 μg to about 1000 μg per gram of composition.

14. The pharmaceutical composition of claim **12** wherein said effective amount comprise from about 0.1 μg to about 500 μg per gram of composition.

15. 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 having the formula:

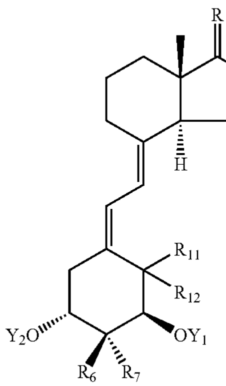


16. A pharmaceutical composition containing an effective amount of 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 together with a pharmaceutically acceptable excipient.

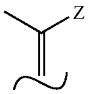
17. The pharmaceutical composition of claim **15** wherein said effective amount comprises from about 0.01 μg to about 1000 μg per gram of composition.

18. The pharmaceutical composition of claim **15** wherein said effective amount comprises from about 0.1 μg to about 500 μg per gram of composition.

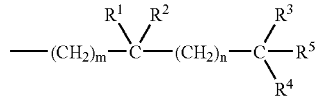
19. A method of treating psoriasis comprising administering to a subject with psoriasis an effective amount of a 17(20)-dehydro vitamin D compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen, where R_6 and R_7, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or R_6 and R_7 when taken together may represent the group $—(CH_2)_x—$ where x is an integer from 2 to 5, or R_6 and R_7 when taken together may represent the group $=CR_8R_9$ where R_8 and R_9, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together R_8 and R_9 may represent the group $—(CH_2)_x—$ where x is an integer from 2 to 5, and where the group R represents a side chain represented by the structure



where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, —OY, $—CH_2OY$, —C≡CY and —CH═CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $—COR^5$ and a radical of the structure:



$$—(CH_2)_m—\overset{R^1\ R^2}{\overset{\diagdown\ \diagup}{C}}—(CH_2)_n—\underset{R^4}{\overset{R^3}{C}}—R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group having a general formula $C_kH_{2k}—$ where k is an integer, the group $=CR^2R^3$, or the group $—(CH_2)_p—$ where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $—(CH_2)_q—$,

where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $—CH(CH_3)—$, $—(CH_2)_m—$, $—CR_1R_2—$ or $—(CH_2)_n—$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

20. The method of claim **19** wherein the vitamin D compound is administered orally.

21. The method of claim **19** wherein the vitamin D compound is administered parenterally.

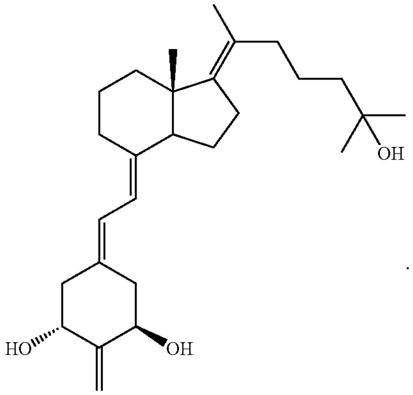
22. The method of claim **19** wherein the vitamin D compound is administered transdermally.

23. The method of claim **19** wherein the vitamin D compound is administered topically.

24. The method of claim **19** wherein the vitamin D compound is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

25. A method of treating psoriasis comprising administering to a subject with psoriasis an effective amount of

17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 having the formula:



26. The method of claim **25** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered orally.

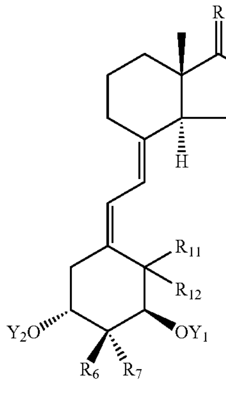
27. The method of claim **25** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered parenterally.

28. The method of claim **25** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered transdermally.

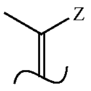
29. The method of claim **25** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered topically.

30. The method of claim **25** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

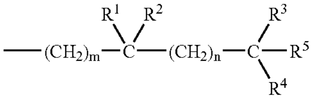
31. A method of treating a disease selected from the group consisting of leukemia, colon cancer, breast cancer, skin cancer or prostate cancer comprising administering to a subject with said disease an effective amount of a 17(20)-dehydro vitamin D compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen, where R_6 and R_7, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or R_6 and R_7 when taken together may represent the group $-(CH_2)_x-$ where x is an integer from 2 to 5, or R_6 and R_7 when taken together may represent the group $=CR_8R_9$ where R_8 and R_9, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together R_8 and R_9 may represent the group $-(CH_2)_x-$ where x is an integer from 2 to 5, and where the group R represents a side chain represented by the structure



where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, —OY, $-CH_2OY$, —C≡CY and —CH═CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $-COR^5$ and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ R^2}{\overset{\diagdown\ \diagup}{C}}-(CH_2)_n-\overset{R^3}{\underset{R^4}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group having a general formula $C_kH_{2k}-$ where k is an integer, the group $=CR^2R^3$, or the group $-(CH_2)_p-$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $-(CH_2)_q-$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $-CH(CH_3)-$, $-(CH_2)_m-$, $-CR_1R_2-$ or $-(CH_2)_n-$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

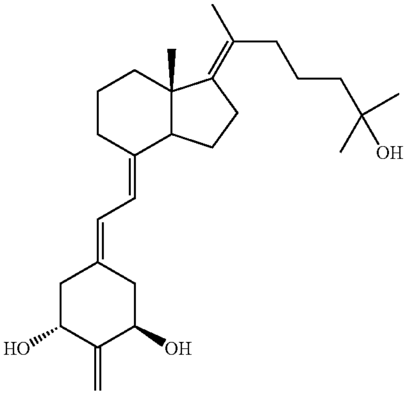
32. The method of claim **31** wherein the vitamin D compound is administered orally.

33. The method of claim **31** wherein the vitamin D compound is administered parenterally.

34. The method of claim **31** wherein the vitamin D compound is administered transdermally.

35. The method of claim **31** wherein the vitamin D compound is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

36. A method of treating a disease selected from the group consisting of leukemia, colon cancer, breast cancer, skin cancer or prostate cancer comprising administering to a subject with said disease an effective amount of 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 having the formula:



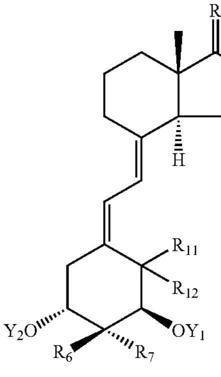
37. The method of claim **36** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered orally.

38. The method of claim **36** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered parenterally.

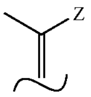
39. The method of claim **36** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered transdermally.

40. The method of claim **36** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

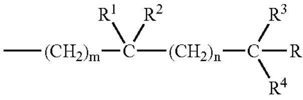
41. A method of treating an autoimmune disease selected from the group consisting of multiple sclerosis, lupus, diabetes mellitus, hot versus graft rejection, and rejection of organ transplants, comprising administering to a subject with said disease an effective amount of a 17(20)-dehydro vitamin D compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen, where R_6 and R_7, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or R_6 and R_7 when taken together may represent the group —$(CH_2)_x$— where x is an integer from 2 to 5, or R_6 and R_7 when taken together may represent the group $=CR_8R_9$ where R_8 and R_9, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together R_8 and R_9 may represent the group —$(CH_2)_x$— where x is an integer from 2 to 5, and where the group R represents a side chain represented by the structure



where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, —OY, —CH_2OY, —C≡CY and —CH═CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR^5 and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ \ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5}alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group having a general formula C_kH_{2k}— where k is an integer, the group $=CR^2R^3$, or the group —$(CH_2)_p$—, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group —$(CH_2)_q$—,

where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —$CH(CH_3)$—, —$(CH_2)_m$—, —CR_1R_2— or —$(CH_2)_n$— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

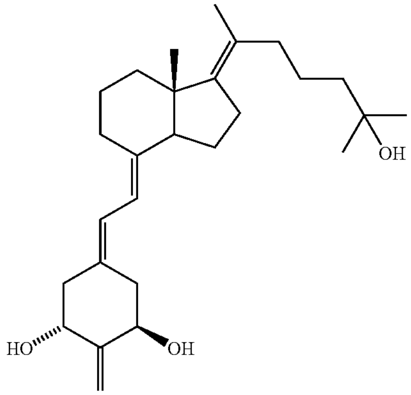
42. The method of claim **41** wherein the vitamin D compound is administered orally.

43. The method of claim **41** wherein the vitamin D compound is administered parenterally.

44. The method of claim **41** wherein the vitamin D compound is administered transdermally.

45. The method of claim **41** wherein the vitamin D compound is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

46. A method of treating an autoimmune disease selected from the group consisting of multiple sclerosis, lupus, diabetes mellitus, host versus graft rejection, and rejection of organ transplants, comprising administering to a subject with said disease an effective amount of 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 having the formula:



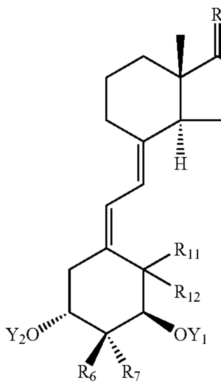
47. The method of claim **46** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered orally.

48. The method of claim **46** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered parenterally.

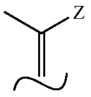
49. The method of claim **46** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered transdermally.

50. The method of claim **46** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

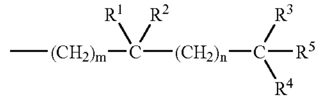
51. A method of treating an inflammatory disease selected from the group consisting of rheumatoid arthritis, asthma, and inflammatory bowel diseases, comprising administering to a subject with said disease an effective amount of a 17(20)-dehydro vitamin D compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen, where R_6 and R_7, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or R_6 and R_7 when taken together may represent the group $—(CH_2)_x—$ where x is an integer from 2 to 5, or R_6 and R_7 when taken together may represent the group $=CR_8R_9$ where R_8 and R_9, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together R_8 and R_9 may represent the group $—(CH_2)_x—$ where x is an integer from 2 to 5, and where the group R represents a side chain represented by the structure



where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, —OY, $—CH_2OY$, —C≡CY and —CH═CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $—COR^5$ and a radical of the structure:



$$—(CH_2)_m—\overset{R^1\ R^2}{C}—(CH_2)_n—\underset{R^4}{\overset{R^3}{C}}—R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group having a general formula $C_kH_{2k}—$ where k is an integer, the group $=CR^2R^3$, or the group $—(CH_2)_p—$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $—(CH_2)_9—$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $—CH(CH_3)—$, $—(CH_2)_m—$, $—CR_1R_2—$ or $—(CH_2)_n—$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

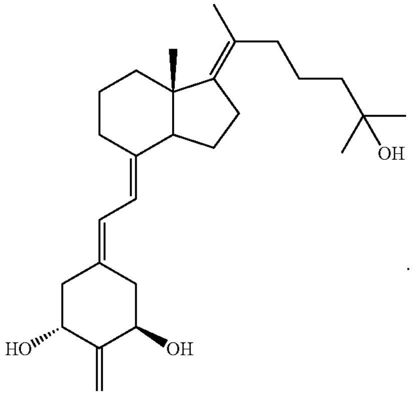
52. The method of claim **51** wherein the vitamin D compound is administered orally.

53. The method of claim **51** wherein the vitamin D compound is administered parenterally.

54. The method of claim **51** wherein the vitamin D compound is administered transdermally.

55. The method of claim **51** wherein the vitamin D compound is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

56. A method of treating an inflammatory disease selected from the group consisting of rheumatoid arthritis, asthma, and inflammatory bowel diseases, comprising administering to a subject with said disease an effective amount of 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 having the formula:



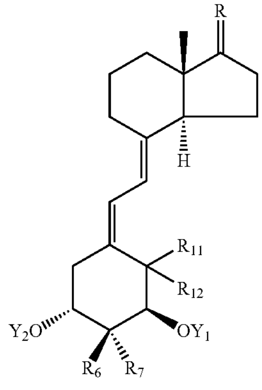
57. The method of claim **56** wherein 17(E)-1α, 25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered orally.

58. The method of claim **56** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered parenterally.

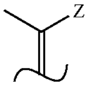
59. The method of claim **56** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered transdermally.

60. The method of claim **56** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

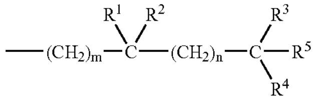
61. A method of treating a skin condition selected from the group consisting of wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration and insufficient sebum secretion which comprises administering to a subject with said skin condition an effective amount of a 17(20)-dehydro vitamin D compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen, where R_6 and R_7, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or R_6 and R_7 when taken together may represent the group $-(CH_2)_x-$ where x is an integer from 2 to 5, or R_6 and R_7 when taken together may represent the group $=CR_8R_9$ where R_8 and R_9, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together R_8 and R_9 may represent the group $-(CH_2)_x-$ where x is an integer from 2 to 5, and where the group R represents a side chain represented by the structure



where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, —OY, $-CH_2OY$, —C≡CY and —CH═CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $-COR^5$ and a radical of the structure:



$$-(CH_2)_m-\overset{R^1\ R^2}{C}-(CH_2)_n-\underset{R^4}{\overset{R^3}{C}}-R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group having a general formula $C_kH_{2k}-$ where k is an integer, the group $=CR^2R^3$, or the group $-(CH_2)_p-$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $-(CH_2)_q-$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $-CH(CH_3)-$, $-(CH_2)_m-$, $-CR_1R_2-$ or $-(CH_2)_n-$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

62. The method of claim **61** wherein the vitamin D compound is administered orally.

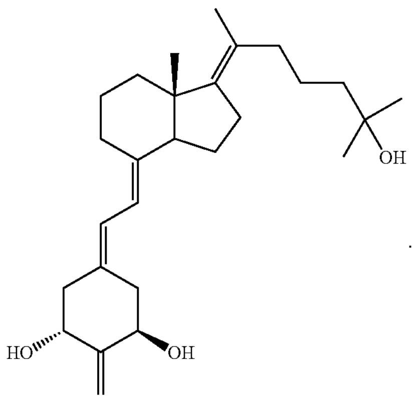
63. The method of claim **61** wherein the vitamin D compound is administered parenterally.

64. The method of claim **61** wherein the vitamin D compound is administered transdermally.

65. The method of claim **61** wherein the vitamin D compound is administered topically.

66. The method of claim **61** wherein the vitamin D compound is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

67. A method of treating a skin condition selected from the group consisting of wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration and insufficient sebum secretion which comprises administered to a subject with said skin condition an effective amount of 17(E)-1α, 25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 having the formula:



68. The method of claim **67** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered orally.

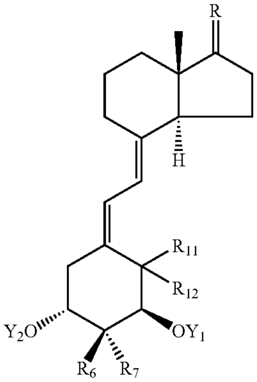
69. The method of claim **67** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered parenterally.

70. The method of claim **67** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered transdermally.

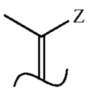
71. The method of claim **67** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered topically.

72. The method of claim **67** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

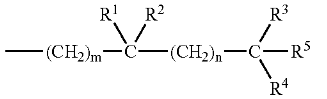
73. A method of treating renal osteodystrophy comprising administering to a subject with renal osteodystrophy an effective amount of a 17(20)-dehydro vitamin D compound having the formula:



where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen, where R_6 and R_7, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or R_6 and R_7 when taken together may represent the group $—(CH_2)_x—$ where x is an integer from 2 to 5, or R_6 and R_7 when taken together may represent the group $=CR_8R_9$ where R_8 and R_9, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together R_8 and R_9 may represent the group $—(CH_2)_x—$ where x is an integer from 2 to 5, and where the group R represents a side chain represented by the structure



where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, —OY, $—CH_2OY$, —C≡CY and —CH═CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $—COR^5$ and a radical of the structure:



$$—(CH_2)_m—\overset{R^1\ \ R^2}{C}—(CH_2)_n—\underset{R^4}{\overset{R^3}{C}}—R^5$$

where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group having a general formula $C_kH_{2k}—$ where k is an integer, the group $=CR^2R^3$, or the group $—(CH_2)_p—$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $—(CH_2)_q—$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $—CH(CH_3)—$, $—(CH_2)_m—$, $—CR_1R_2—$ or $—(CH_2)_n—$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

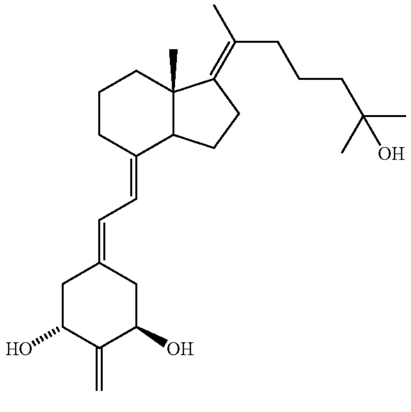
74. The method of claim **73** wherein the vitamin D compound is administered orally.

75. The method of claim **73** wherein the vitamin D compound is administered parenterally.

76. The method of claim **73** wherein the vitamin D compound is administered transdermally.

77. The method of claim **73** wherein the vitamin D compound is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

78. A method of treating renal osteodystrophy comprising administering to a subject with renal osteodystrophy an effective amount of 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 having the formula:



79. The method of claim **78** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered orally.

80. The method of claim **78** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered parenterally.

81. The method of claim **78** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered transdermally.

82. The method of claim **78** wherein 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 is administered in a dosage of from about 0.01 μg/day to about 1000 μg/day.

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